CSGB

CENTRE FOR **STOCHASTIC GEOMETRY**
AND ADVANCED **BIOIMAGING**

Annual Report 2012


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From the Workshop on Geometry and Statistics: Manifolds and Stratified Spaces that was held 8-12 October 2012 at Sandbjerg Estate in the southern part of Denmark. Group photo in front of the manor house. The workshop was co-financed by an International Network Programme grant from the Danish Council of Scientific Research and Innovation.

INTRODUCTION

Centre for Stochastic Geometry and Advanced Bioimaging – CSGB – is a VKR Centre of Excellence, funded by the Villum Foundation by a donation of 25 mill DKK. The Centre was established in 2010 as an interdisciplinary collaboration between the Universities of Aarhus (AU), Aalborg (AAU) and Copenhagen (KU), involving Department of Mathematics (AU), Clinical Institute (AU), Department of Mathematical Sciences (AAU) and Department of Computer Science (KU).

The aim of CSGB is to develop new **mathematical, statistical and computational methods** of analyzing advanced bioimaging data. A particular focus is on the analysis of molecular microscopy data. Many of the methods utilize the recent developments in stochastic geometry, a discipline at the borderline between mathematics and statistics.

With this annual report, I want to inform our colleagues, potential research students, the Danish funding partner and the Universities of Aarhus, Aalborg and Copenhagen about organizational issues, research and other centre activities that took place at CSGB in 2012.

The year of 2012 became a period of consolidation. A few changes were made in the organization of the research projects (p. 11). Two postdocs and three Ph.D. students were hired in 2012 (p. 12-13). The resulting staff of CSGB consisted in 2012 of 7 professors, 13 associate professors, 10 postdocs/assistant professors and 12 Ph.D. students. A total of 21 researchers were either partly or fully funded by CSGB. Additional funding was attracted from a number of sources, including a **Velux Visiting Professorship** at AAU May-June 2012 and co-funding of equipment, positions and workshops from the Ministry of Science, Innovation and Higher Education, the Danish Council for Strategic Research, the Danish Centre for Scientific Computing and the Universities of Aarhus, Aalborg and Copenhagen. Further details are given on p. 12.

During the three years since CSGB started, the involved four research groups have grown together. Especially, the collaborative projects concerning minicolumns and vesicles have made very important progress during the last months. A number of young researchers contribute in a decisive manner to the success of CSGB. In this report, we give a portrait of three of these researchers: Aasa Feragen, Ege Rubak and Anne Marie Svane (pp. 19-21). In 2012, they have obtained original scientific results in the projects **digital stereology, spatial and spatio-temporal point processes** and **random shapes**. The full description of research results in 2012 may be found on pp. 22-39.

In 2012, the stochastic geometry group and the image group arranged the workshop **Geometry and Statistics in Bioimaging: Manifolds and Stratified Spaces**, 8 - 12 October 2012, Sandbjerg Estate. The background for arranging this workshop was the fact that computer vision and biomedical image analysis communities generate a wide range of geometric problems that never make it to the pure mathematicians. On the other hand, important advances in statistics on manifolds and stratified spaces, developed in the mathematical statistics community, often remain unnoticed among image analysis researchers. It was the goal of this workshop to strengthen the mathematical imaging community by forming an international network of researchers working to advance statistics on manifolds and stratified spaces.

March 2013
Eva B. Vedel Jensen

ORGANIZATION AND STAFF

The four research group leaders (from left to right): Mads Nielsen (KU), Eva B. Vedel Jensen (AU-math), Jens R. Nyengaard (AU-bio) and Jesper Møller (AAU).

THE FOUR PARTICIPATING RESEARCH GROUPS

CSGB comprises the following four Danish research groups:

AU-math

The stochastic geometry group, Department of Mathematics, AU - led by Professor Eva B. Vedel Jensen (EBVJ).

The group comprises two professors and four associate professors with competences in

- stereology
- stochastic geometry
- topology
- singularity theory
- statistical inference for high dimensional data

AU-bio

The biomedical group, Stereology and EM Research Laboratory, Clinical Institute, AU - led by Professor Jens R. Nyengaard (JRN).

The group comprises one professor and four associate professors with competences in

- light microscopy
- fluorescence microscopy
- electron microscopy, especially cryo-EM

AAU

The spatial statistics group, Department of Mathematical Sciences, AAU - led by Professor Jesper Møller (JM).

The group comprises two professors, two associate professors and one assistant professor with competences in

- inhomogeneous point processes
- spatio-temporal point processes
- generalized mixed models
- MCMC
- perfect simulation

KU

The image group, Department of Computer Science, KU - led by Professor Mads Nielsen (MN).

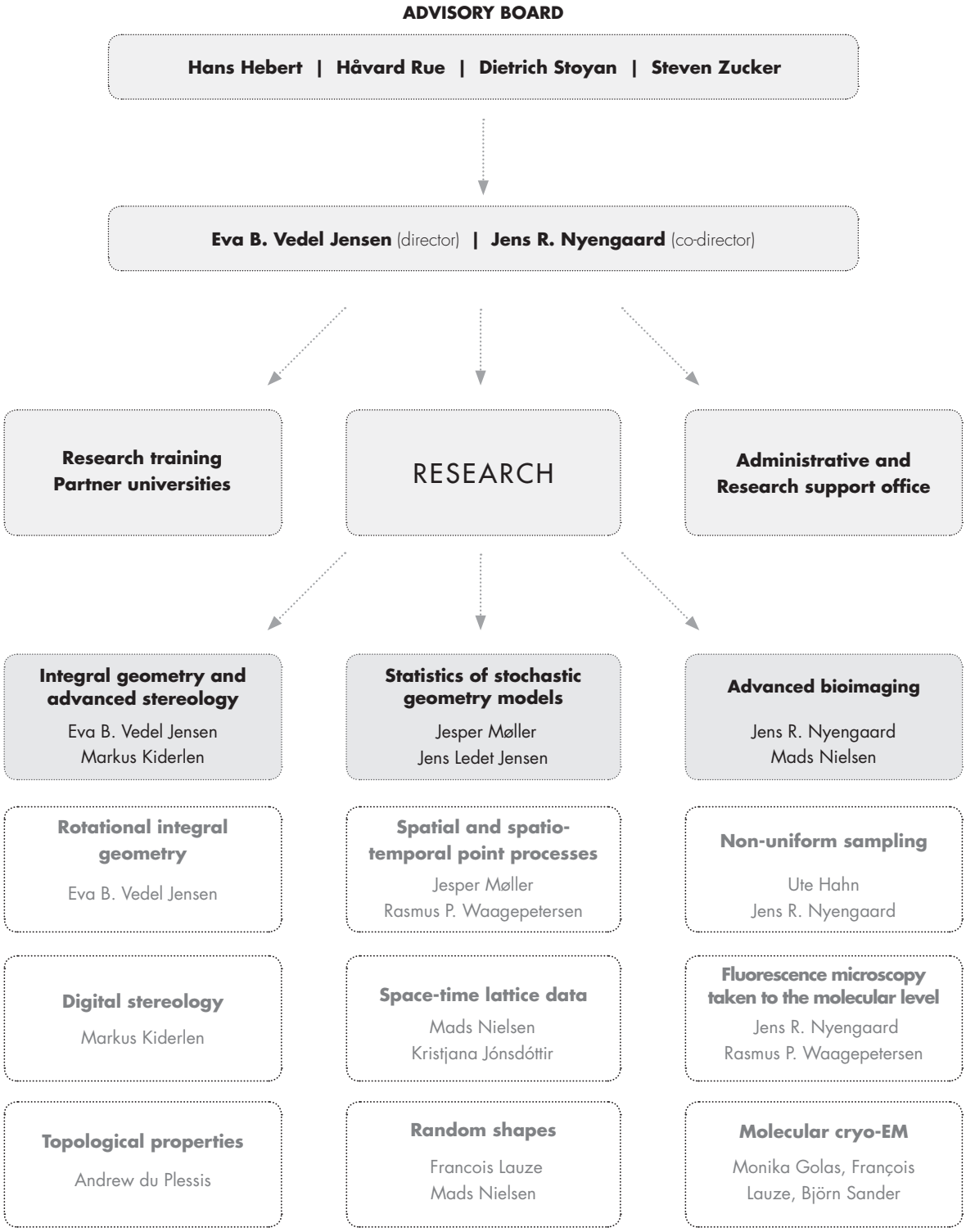
The group participating in CSGB comprises two professors and four associate professors with competences in

- stochastic shape modelling
- Bayesian inference
- partial differential equations for image analysis
- application to biomedical problems

OVERVIEW OF ORGANIZATION

CSGB is organized along three streams of research, coordinated by senior scientists of the Centre. Each stream contains three research projects; the principal investigator(s) of each research project is (are) indicated in the diagram below.

Compared to the corresponding diagram that appeared in the original Centre proposal, **Rasmus P. Waagepetersen** substitutes Merete Raarup in the *Fluorescence microscopy taken to the molecular level* project, while **Kristjana Jónsdóttir** substitutes Jakob G. Rasmussen in the *Space-time lattice data* project. **Ute Hahn** has been included as principal investigator in the project *Non-uniform sampling*.



COLLABORATION - FUNDING - NETWORKS

Velux Visiting Professorship
A Velux Visiting Professorship has been obtained for Professor **Yongtao Guan**, University of Miami, for a research stay at AAU May - June 2012. CSGB has during 2012 also received co-funding of several postdoc and Ph.D. positions from the Universities of Aalborg, Aarhus and Copenhagen, the Danish Council for Strategic Research and the MIND Centre, AU.

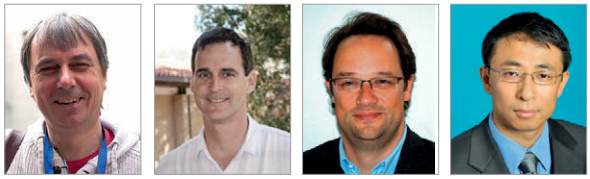
VILLUM FONDEN

Additional funding
The international collaboration with researchers that share a common interest in statistics on manifolds and stratified spaces has been strengthened during 2012 by the organization of the **Workshop on Geometry and Statistics in Bioimaging: Manifolds and Stratified Spaces**, 8 - 12 October 2012, Sandbjerg Estate. In 2012, the Ministry of Science, Innovation and Higher Education supported this initiative with 353.477 DKK. A special issue of Journal of Mathematical Imaging and Vision with papers from the workshop is in the process of being edited.

Research network
A number of researchers at CSGB participate in the research network represented by the **International Society for Stereology**. Also in 2012, a stereology workshop has been arranged in Bern, supported by the University of Bern, and a Ph.D. course on stereology has been organized at Sandbjerg Estate, supported by Aarhus University.

International collaboration
The stochastic geometry group, Department of Mathematics, Karlsruhe Institute of Technology, is an important international research partner of CSGB. The Karlsruhe group takes active part in the CSGB research stream entitled **Integral geometry and advanced stereology**.

Key collaborator
Since its start, CSGB has had a number of international visitors/collaborators. A key collaborator is Professor **Adrian Baddeley,** University of Western Australia and CSIRO Mathematics, Informatics and Statistics, Perth, Australia. Since Adrian Baddeley has played a crucial role for the development of three of the four research groups that participate in CSGB, we are right now bringing forward to the Faculty of Science and Technology, AU, the prososal to appoint him as adjunct professor at AU.



Four researchers that have played an important role for CSGB in 2012 (from left to right): invited speaker Professor Herbert Edelsbrunner (Duke University, USA; Institute of Science and Technology, Austria), key collaborator Professor Adrian Baddeley (University of Western Australia and CSIRO Mathematics, Informatics and Statistics, Perth), workshop organizer and collaborator Professor Matthias Ochs (University of Bern) and Velux Visiting Professor Yongtao Guan (University of Miami).

NEW APPOINTMENTS IN 2012

Ali Hoseinpoor Rafati (AU-bio)
Ali Hoseinpoor Rafati has been associated to CSGB since August 2011, first as a research assistant at AU-bio, but since June 2012 as a Ph.D. student at AU-bio. Ali has experience from participating in research projects at Tehran University of Medical Sciences. He is part of the interdisciplinary team at CSGB working with developing tools for analyzing the minicolumn hypothesis relating to the structure of the human cerebral cortex. Methods from **Spatial and spatio-temporal point processes** are involved in this project.

NEW APPOINTMENTS IN 2012

Astrid Kousholt (AU-math)
Astrid Kousholt has been a Ph.D. student at AU-math since 1 September 2012. Astrid has a bachelor degree (2011) in mathematics from Department of Mathematics, AU. Her Ph.D. project concerns tensor valuations in stochastic geometry and stereology. Both **Rotational integral geometry** and **Digital stereology** are involved in her project. In 2008, she participated in the Indian Network for Development of Exchange programme.

Matthew Liptrot (KU)
Matthew Liptrot is a very experienced researcher in bioimaging. He was awarded the Ph.D. degree from Imperial College London in 2011 with a thesis entitled Image Processing in Diffusion MRI Tractography. Since 1 August 2012, he has held a postdoc position at KU. Matthew is working in the CSGB project **topological properties**. Graph kernel methods on connectivity graphs are used in the analysis of DWI data to investigate the connectivity of the human brain.

Mahdieh Khanmohamadi (KU)
Mahdieh Khanmohamadi started in February 2012 as a Ph.D. student at the Image Group, KU. Her Ph.D. project represents a collaborative project between KU and AU-bio. The project concerns vesicle analysis in electron microscope images and is a subproject of the CSGB project **Digital stereology**. Mahdieh has a master of science degree in bioengineering and image processing from University of Tehran. She has also studied computational science and engineering at Halmstad University.

Robert Jacobsen (AAU)
Robert Jacobsen started in January 2012 in a postdoc position at AAU. He has a master degree in mathematics and statistics from Aalborg and Aarhus Universities. Subsequently, Robert Jacobsen obtained a Ph.D. degree from Aalborg University with a thesis entitled Digital Painting Analysis. Robert is working in the CSGB project **Spatial and spatio-temporal point processes** where he investigates the use of spatial point processes in magnetic resonance imaging (MRI). Besides, he is a skilled swimmer.

HIGHLIGHTS 2012

S^{4}G - International Conference on Stereology, Spatial Statistics and Stochastic Geometry
Prague, Czech Republic, 25 June - 28 June 2012

One of the highlights in 2012 was the S^{4}G Conference on Stereology, Spatial Statistics and Stochastic Geometry, Prague, 25 – 28 June 2012. Three of the four research groups at CSGB were represented at this conference. **Eva B. Vedel Jensen** (AU-math) gave the opening lecture entitled *Stereology of tensors* in the beautiful aula of the renovated historical building of the Faculty of Mathematics and Physics, Charles University in Prague. **Jesper Møller** (AAU) gave a plenary lecture entitled *Statistical aspects of determinantal point processes*. **Jens R. Nyengaard** (AU-bio) arranged a minisymposium on biomedical stereology and gave himself a lecture entitled *Brain cells, synapses and vesicles*. At the minisymposium on model validation for spatial point processes, **Ute Hahn** (AU-math) presented her new results concerning *Nonparametric tests of inhomogenous spatial point process model classes*. Finally, **Mohammad Ghorbani** (AAU) gave a lecture on *Aspects of second-order analysis of structured inhomogeneous spatio-temporal point processes* at the minisymposium on spatio-temporal modelling and statistics.

Midterm Evaluation of CSGB

An important event in 2012 for the CSGB staff was the midterm evaluation. On this occasion, a 46 page long midterm report was produced. This report and a supplementary report from the advisory board of CSGB were submitted to the Villum Foundation early November 2012. A minisymposium was held 13 October 2012 where the following CSGB researchers gave lectures

- **Markus Kiderlen** (AU-math): *Digital stereology*
- **Rasmus Waagepetersen** (AAU): *New estimating functions for spatial point processes*
- **Aasa Feragen** (KU): *Random shapes - towards a theory of statistical tree-shape analysis*
- **Monika Golas** (AU-bio): *Molecular cryo-EM*
- **Ina Trolle Andersen** (AU-math/bio): *The proportionator*
- **Katrine Hommelhoff Jensen** (KU): *Reconstruction algorithms in cryo-EM*
- **Ali Hoseinpoor Rafati** (AU-bio): *Minicolumns*

At the minisymposium, the advisory board played a very constructive and active role. The minisymposium is also shortly mentioned elsewhere in this annual report (p. 48).

Workshop on Geometry and Statistics: Manifolds and Stratified Spaces
Sandbjerg Estate, Denmark, 8-12 October 2012

For the staff of CSGB, this workshop meant a unique opportunity for presenting their research results in an international expert forum. **Anne Marie Svane** (AU-math) gave a lecture on *Local digital estimators for the integrated mean curvature*. These results are further described in the section on Digital stereology, see pp. 24-25. **Stefan Sommer** (KU) presented his results on *Sufficiently large subsets of diffeomorphism manifolds* while **Aasa Feragen** (KU) talked about *Uniqueness of geodesics between geometric trees*. See also the section on Random shapes, pp. 32-33. Finally, **Eva B. Vedel Jensen** (AU-math) discussed new results for *Spatial point processes on linear networks*. The illustration at the front page of this annual report is inspired by this lecture.

26th International Biometric Conference
Kobe, Japan, 26 – 30 August 2012

It was a great pleasure for the local organizers to welcome all delegates, their families and friends to the XXVIth International Biometric Conference (IBC 2012) being hosted by the Japanese Region in Kobe. It was nearly thirty years since they hosted the previous IBC held in Japan in Tokyo in 1984. The Kobe International Convention Centre provides excellent spaces for formal meetings/scientific sessions and informal conversations/networking activities which are an essential part of every IBC. The task of the LOC was made particularly difficult after the natural disaster which stuck northern Japan in early 2011. The Japanese Region very much appreciated the concern shown by members from around the world for their welfare under incredibly difficult conditions.

Rasmus Waagepetersen (AAU) was an invited speaker at this conference. The title of his talk was *Optimal estimation of the intensity function of a spatial Cox process*.

RESEARCH

BACKGROUND AND MISSION

In microscopy, there has in recent years been an increasing interest in going beyond a global stereological analysis of the biostructure under study. Such a global analysis typically results in estimates of total cell number and mean cell volume. For example, in stereological studies of the cerebral cortex of the human brain of subjects with dementia or schizophrenia, no major changes in total cell number have been found. Some postmortem studies of schizophrenia have, however, reported changes in the spatial arrangement of cells in specific cortical areas. Also, disease-caused changes in tissue may leave the size distribution of cells unaffected and instead affect shape or orientation distributions. These examples show that there is a need for developing flexible local stereological methods of describing cell **orientation distribution, shape distribution, symmetry**, etc.

During the last decades, stochastic geometry has provided a wealth of stochastic models. Most of these models have point processes as fundamental building blocks. Until now, stochastic geometry models have not had the influence in bioimaging, especially in quantitative microscopy, that they deserve. It is therefore necessary to explore the use of stochastic geometry models more extensively in microscopy and generelly in bioimaging. In particular, the **obvious potential of point process models** in the analysis of spatial arrangements of cells has not yet been thoroughly investigated.

On the other hand, quantitative microscopy and bioimaging also challenge stochastic geometry. The intriguing mathematical and statistical questions, arising from the study of the connection between objects in the real world and their **digital representations,** are still not fully understood. Imaging data (e.g. shapes in 2D and 3D space) are often most naturally modelled on manifolds and there is a need to **translate statistical notions** and methods into the manifold world. The new advanced experiments within microscopy that give access to the molecular level, including fluorescence microscopy and cryo-EM, require the development of new mathematical and geometrical/statistical methods of analysis.

FIVE SPECIFIC GOALS OF CSGB

Since the start of CSGB in April 2010, the goals of CSGB have not changed. They have now been crystallized in the five specific goals presented below.

- to develop a theory of rotational integral geometry of tensor valuations and use this theory in local stereological estimation of position, shape and orientation
- to obtain a deeper understanding of the quantitative properties that are estimable from digital images
- to develop statistical inference for a number of new stochastic geometry models for point processes and random fields
- to contribute significantly to the development of statistical inference on shape spaces
- to develop new mathematical and statistical methods of analyzing concrete bioimaging data, including fluorescence microscopy data and cryo-EM data

PORTRAIT: AASA FERAGEN

Academic career

Aasa Feragen is 31 years old and originally from Norway. She has a master degree from 2005 in Geometric Topology from University of Helsinki and a Ph.D. degree from 2009 in Differential topology and singularity theory. A major part of the Ph.D. study took place at Department of Mathematics, Aarhus University, Denmark. She has now a position as Freja fellow and assistant professor (with tenure track) at the Image Group, Department of Computer Science, University of Copenhagen. Right now, she is on leave from this position and postdoctoral fellow at the MPI for Intelligent Systems and MPI for Developmental Biology, Tübingen, Germany. She has international collaborators in Canada, Germany, the Netherlands and USA. She has obtained a number of grants, including grants from Helsinki University Science Foundation, the Lundbeck Foundation and the Danish Council for Independent Research. Aasa Feragen has four journal publications and eleven publications in refereed conference proceedings.

Research

Since the establishment of CSGB in 2010, Aasa Feragen has contributed decisively to the research on tree-shaped structures in the **Random shapes** project. A mathematical framework for spaces of tree-structured shapes has been developed. Aasa has also played a very active role in the workshop **Geometry and Statistics in Bioimaging: Manifolds and Stratified Spaces**, 8 - 12 October 2012, Sandbjerg Manor.

Future

About the future, Aasa says: "I want to have a dynamic collaboration with medical doctors, engineers and computer scientists so that our mathematical modelling can be used to solve real problems in a way that can be implemented in practice. With a theoretical background as mine, it is a unique satisfaction to develop models that actually solve a problem in practice and not only in theory. So I hope that I can continue in the research area of mathematical modelling in bioimaging. It is also important for me to communicate my research results and I really like to teach. Right now, I work with very engaged and talented students. This is exciting and inspiring. In 10 years time, I hope that I will be able to support myself and a couple of Ph.D. students; not too many since I want to have time to actively participate in the research myself. This is actually why I have chosen this job – to be able to do research."

Aasa Feragen
Aasa Feragen is a Freja fellow and assistant professor (with tenure track) at the Image Group, Department of Computer Science, University of Copenhagen. Aasa is working in the CSGB project **Random shapes** where she is developing a mathematical (and statistical) framework for spaces of tree-structured shapes.

PORTRAIT: ANNE MARIE SVANE

Anne Marie Svane
Anne Marie Svane is a postdoc at the Stochastic Geometry Group, Department of Mathematics, Aarhus University. Anne Marie is working in the CSGB project **Digital stereology** where she is developing local digital algorithms.

Academic career

Anne Marie Svane is 29 years old. She has a master degree (2009) and a Ph.D. degree (2011) in algebraic topology from Department of Mathematics, Aarhus University. During her Ph.D. study, she had a three months stay at Oxford University as a visiting Ph.D. student. Immediately after the Ph.D. defense she was hired as a postdoc at CSGB where she has been using her theoretical background in the CSGB research project **Digital stereology**. She has been very successful doing this and written three scientific papers on this topic in this short time period. At the same time, she has kept the contact to theoretical algebraic topology and written three scientific papers on this topic based on her thesis. This is an unusually high number of papers in mathematics during a 1½ year period. In 2012, Anne Marie gave six scientific talks, three of these at international meetings. Recently, she obtained a travel grant from the Carlsberg Foundation. The plan is to visit the stochastic geometry group in Karlsruhe during a 10 months period.

Research

One of the main contributions of Anne Marie to the research at CSGB has been her paper on local digital algorithms for estimating the integrated mean curvature. Some of the theoretical results in this paper show why we have been unable to find an improved estimator of the integral of mean curvature.

Future

About the future, Anne Marie says: "My plans for the near future is to spend 10 months in Karlsruhe. When I return, there are still six months left of my present appointment. My further plans will be made during these months. Whether I am interested in further stays abroad and possibly an international scientific carrier abroad will probably depend on my experiences in Karlsruhe. Right now, a permanent university position seems attractive to me, but I know that this can be hard to obtain. I like university teaching very much and I have really enjoyed working with digital stereology. In this area I get to use both my geometric intuition and my theoretical background in geometry and topology. At the same time my work seems relevant, having applications other places in science. However, I also feel that it will soon be time to seek new challenges research-wise. Here I hope to benefit from the stay in Karlsruhe."

PORTRAIT: EGE RUBAK

Academic career

Ege Rubak is 31 years old. He obtained a master degree (2007) in mathematics with a thesis on *Central limit theorems for weakly dependent stochastic processes* and a Ph.D. degree (2010) in statistics with a thesis entitled *Likelihood based inference and diagnostics for spatial data models* from Department of Mathematical Sciences, Aalborg University. During his Ph.D. study, Ege has been a visiting Ph.D. student at University of Chicago and University of Western Australia. Ege was a CSGB postdoc in 2010-2012 and is now assistant professor at Department of Mathematical Sciences, Aalborg University. He has obtained various travelling grants and has a very fruitful international collaboration with professor Adrian Baddeley, University of Western Australia, professor Jean-François Coeurjolly, Grenoble University, and professor Frédéric Lavancier, University of Nantes. Ege has written eight scientific papers and given a number of talks at international conferences.

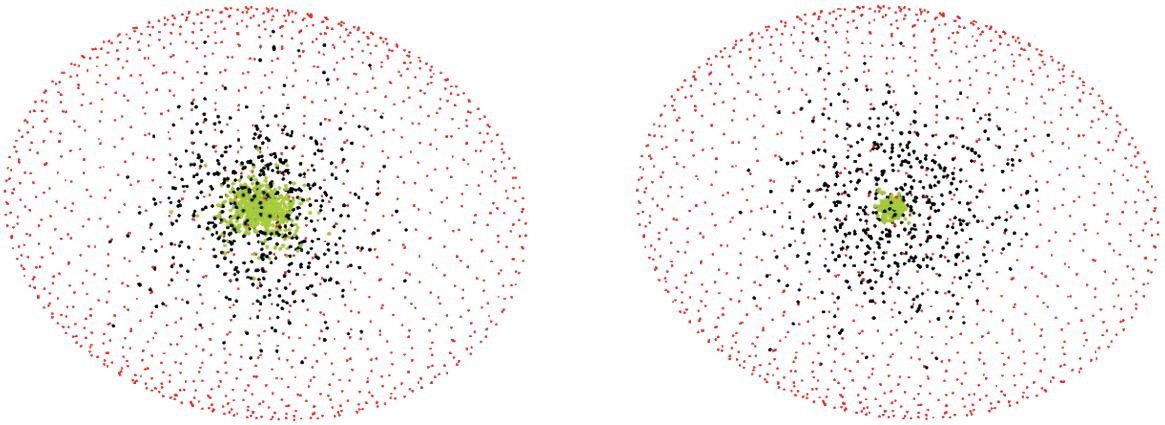
Research

Ege Rubak has taken part in the collaborative CSGB project **Fluorescence microscopy taken to the molecular level** that has involved the spatial statistics group (AAU), the biomedical group (AU-bio) and the stochastic geometry group (AU-math). A statistical model on the pixel level which includes measurement noise in all three images collected in FRET microscopy has been developed. Besides, he has contributed to the CSGB project **Spatial and spatio-temporal point processes** with six scientific papers.

Future

About the future, Ege says: "My current employment as an assistant professor at Aalborg University terminates in 2015. After this point, I don't have a clear career plan at the moment. On one hand, I hope to be able to continue my career in academia, since it is a very inspiring working environment, which includes working with experts from all over the globe. I would like to continue to develop theoretical statistical methods and models, and make these available for the wider research community in statistical software that can be applied in practical work. I consider it to be very privileged to work in academia where you are free to follow your research interests to a wide extent as long as your results are published in peer reviewed journals. On the other hand, research can also be very frustrating when you don't obtain the results you were expecting or hoping for. Furthermore, the publication pressure and increasing importance of obtaining external funding can be somewhat overwhelming for a young researcher."

Ege Rubak
Ege Rubak is an assistant professor at the Spatial Statistics Group, Department of Mathematical Sciences, Aalborg University. Ege has worked in the CSGB projects **Fluorescence microscopy taken to the molecular level** and **Spatial and spatio-temporal point processes.**



Estimation of the centre of gravity, using systematic random sets of $N = 3$ or $N = 7$ lines for the left and right panels, respectively. The red dots visualize an ellipsoid; the black dots are the initially chosen origins distributed according to a truncated normal distribution. The green dots show the estimated centres of gravity.

RESEARCH | INTEGRAL GEOMETRY AND ADVANCED STEREOLOGY

ROTATIONAL INTEGRAL GEOMETRY

In rotational integral geometry, geometric identities of the following form is considered

$$\int \alpha(K \cap L)\, \mathrm{d}L = \beta(K)$$

where α and β are geometric quantities, K is the spatial object of interest, L is the probe (line, plane, convex body, ...) and dL is the element of the rotation invariant measure on the set of probes. Specific choices of α or β are the **intrinsic volumes**, including ordinary volume, surface area and the Euler-Poincaré characteristic. In rotational integral geometry, L is typically a linear subspace of R^n. For instance, L is a plane passing through a fixed reference point, taken to be the origin.

In Jensen & Rataj (2008), geometric identities of this type were studied with L a linear subspace of R^n and α an intrinsic volume. The corresponding β functional was, however, in Jensen & Rataj (2008) only given as a complicated integral over the normal bundle of K. In close collaboration with Jan Rataj, Charles University, Prague, CSGB researchers have managed to find a **closed form** of the corresponding β functional. This result has now been published in Auneau *et al.* (2012). The inverse problem of expressing the intrinsic volumes of the original spatial structure as a rotational integral of suitably chosen measurements in the sections was already solved in Auneau & Jensen (2010). This corresponds to choosing β as an intrinsic volume and searching for a functional α satisfying the above equation with L a linear subspace. The paper Auneau & Jensen (2010) did, however, not give any solution to the question of whether this functional is **unique**. And this problem is still largely open.

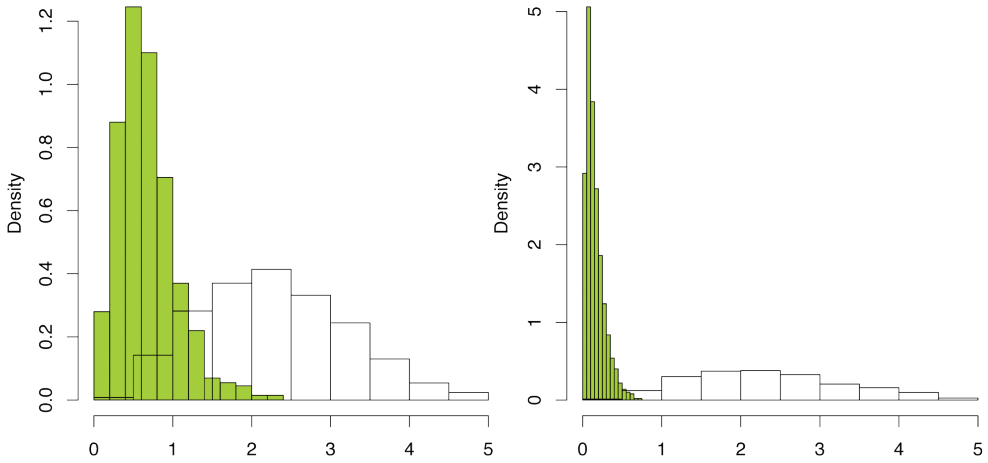
In 2012, the focus has been on further development of rotational integral geometry for **Minkowski tensors**. Minkowski tensors of rank zero are simply the intrinsic

volumes, rank 1 tensors provide information about various types of centres of gravity and rank two tensors contain shape/orientation information. The so-called integrated Minkowski tensors obey a genuine **rotational Crofton formula** (Auneau-Cognacq *et al.*, 2013). The new rotational formula contains a number of interesting special cases important for applications. In Jensen & Ziegel (2012), it is shown how this formula can be used to develop local stereological estimators of classical Minkowski tensors.

During 2012, a local version of the classical **Wicksell's problem** has also been solved (Thórisdóttir & Kiderlen, 2012).

A main task will now be to use the new theory of rotational integral geometry of Minkowski tensors in the development of local stereological methods of estimating cell orientation and shape. Stereology for tensor-valued functionals has a totally different character than stereology for scalar-valued functionals and requires clever 3D sampling. In particular, there are issues of overprojection in thick microscopy sections that need to be taken into account. An obvious line of research to follow will be to restrict the measurements to a slab centred at the reference point of the cell and use **hitting probabilities** in a correction for non-sampling of the peripheral parts of the cell. A similar approach has much earlier been used in the simple situation where cell volume and surface area were to be estimated, see Tandrup *et al.* (1997).

On the theoretical side, it is needed to study the integrated Minkowski tensors further, in particular search for specific parameter values for which the integrated Minkowski tensors can be simplified. The relation to flag measures should be clarified. To make the theory of rotational integral geometry complete, it is also needed to derive a **principal rotational formula**.



The histograms show the distribution of the norms of the initially chosen origins (white bars) and of the estimated centres of gravity (green bars).

Researchers

Eva B. Vedel Jensen
Markus Kiderlen
Astrid Kousholt
Ólöf Thorisdottir
Johanna F. Ziegel

References

Auneau, J. & Jensen, E.B.V. (2010): Expressing intrinsic volumes as rotational integrals. *Adv. Appl. Math.* **45**, 1-11.

Auneau, J., Rataj, J. & Jensen, E.B.V. (2012): Closed form of the rotational Crofton formula. *Math. Nachr.* **285**, 164-180.

Auneau-Cognacq, J., Ziegel, J. & Jensen, E.B.V. (2013): Rotational integral geometry of tensor valuations. *Adv. Appl. Math.* **50**, 429-444.

Jensen, E.B.V. & Rataj, J. (2008): A rotational formula for intrinsic volumes. *Adv. Appl. Math.* **41**, 530-560.

Jensen, E.B.V. & Ziegel, J.F. (2012): Local stereology of tensors. *CSGB Research Reports* **12-11**. Submitted.

Tandrup, T., Gundersen, H.J.G. & Jensen, E.B.V. (1997): The optical rotator. *J. Microsc.* **186**, 108-120.

Thórisdottir, Ó. & Kiderlen, M. (2012): Wicksell's problem in local stereology. *Adv. Appl. Probab.*, to appear.

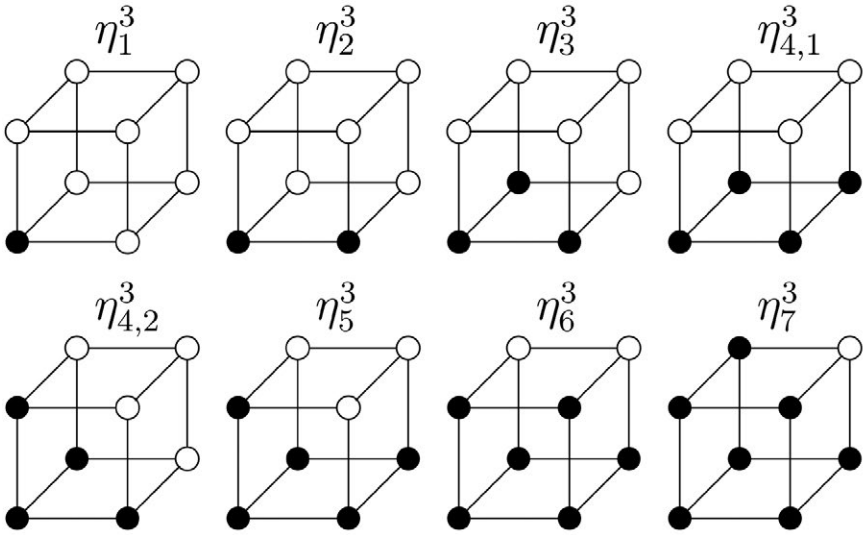


Figure 1: Eight equivalence classes considered in Svane (2012a).

RESEARCH | INTEGRAL GEOMETRY AND ADVANCED STEREOLOGY

DIGITAL STEREOLOGY

This CSGB project deals with the retrieval of characteristics of geometric objects from binary pixel (2D) or voxel (3D) images. Common geometric characteristics of interest for an n-dimensional object K are the **intrinsic volumes**. In this project, we only consider local algorithms based on $2\times 2\times\cdots\times 2$ configuration counts, as these can efficiently be calculated by filtering the image in linear time (Ohser & Mücklich, 2000). There are 2^{2^n} configurations, i.e. combinations of the 2^{2^n} vertices of a $2\times 2\times\cdots\times 2$ cell belonging either to the foreground or the background. If N_l denotes the number of occurrences of the lth configuration in the image, the intrinsic volumes may be estimated by linear combinations of the N_ls with coefficients determined by geometric arguments, discretization of integral formulae, or probabilistic reasoning, respectively.

In this project, we have focused on the analysis of different algorithms, or, equivalently, different choices of coefficients in the linear combinations of the N_ls, with the ultimate goal of finding **optimal coefficients** for the estimation of intrinsic volumes from digital images. The starting point has been a first-order asymptotic formula (Kiderlen & Rataj, 2007, Theorem 5)

$$\lim_{a\to 0+} a^{n-1} EN_l = \int_{S^{n-1}} h_l(v) S(K, \mathrm{d}v) =: c_1,$$

for the case where the lattice is randomized (in a stationary manner). It states that the appropriately scaled average configuration count EN_l is asymptotically an integral, where only the integrand depends on the configuration l, and the object K only enters in the integrating surface area measure. If intrinsic volumes with index $i < n-1$ are considered (such intrinsic volumes can be expressed as curvature integrals), this equation is, however, no longer sufficient, but has to be replaced by higher order formulae. This problem has been solved in Svane (2012a, Corollary 6.1) where the following **second-order expansion** has been derived

$$EN_l = c_1\, a^{1-n} + c_2\, a^{2-n} + o(a^{2-n}),$$

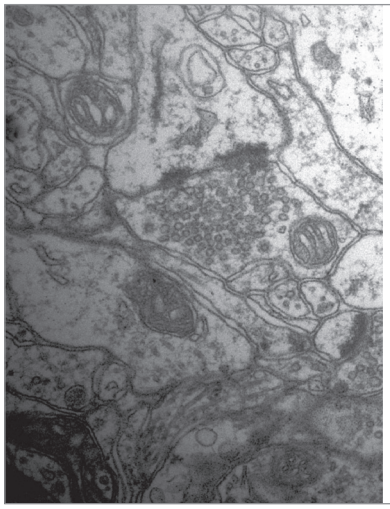
as $a \to 0+$, where c_2 is a surface integral on the boundary of K, whose integrand is a quadratic form with an explicitly known dependence on the principal

directions and curvatures of K at x. The delicate derivation of this result requires that K is an **r-regular set**; a similar formula without such strong smoothness assumptions is not expected to hold.

In 2012, it has also been possible to derive **new asymptotic Miles-type formulae** for Boolean models in the plane with disks as typical particles (Svane, 2012b). In Svane (2012b), numerous generalizations based on refinements of Kiderlen & Rataj (2007) are also treated: non-asymptotic Miles-type approximations for Boolean models when the resolution is high but finite, analogs for standard random sets, speed of convergence when the object's boundary is a differentiable manifold, and, finally, a comparison of existing digital algorithms for the planar case based on these.

The above results are all concerned with binary black+white images, and based on a simplifying digitization model, the so-called Gauss digitization. In applications, the images consist typically of gray-tone or multicolor voxels. A more realistic digitization model for gray-tone images was suggested by Stelldinger & Köthe (2006) where the unavoidable blurring due to image acquisition systems is modeled by a convolution of the continuous image with a point spread function. The resulting gray-tone image can then be thresholded at one or several levels in order to apply the binary methods already developed. We are currently extending our asymptotic theory to this new digitization model, expecting that many results take over, although requiring a finer analysis at certain stages.

To quantify refined geometric properties, **tensor valued generalizations** of intrinsic volumes have been introduced in physical applications (Schröder-Turk *et al.*, 2008, 2010) including implementations of local digital algorithms for their approximation. In the upcoming project period, we plan to compare the asymptotic bias of existing algorithms when applied to planar Boolean models. In the course of these investigations, we also expect to formulate digital Miles-type formulae for planar stationary Boolean models with simple grains.



Vesicles

In addition to the above mentioned plans, we are engaged in a concrete application of digital stereology, involving the development of quantitative methods in combination with serial-section-electron microscopy for estimating the number and position of **synaptic vesicles**. Changes in the function and structure of synaptic connections between neurons are believed to represent one of the major mechanisms behind learning, memory and most physiological functions within the brain.

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References

Kiderlen, M. & Rataj, J. (2007): On infinitesimal increase of volumes of morphological transforms. *Matematika* **53**, 103-127.

Ohser, J. & Mücklich, F. (2000): *Statistical Analysis of Microstructures in Materials Science*. Wiley, New York.

Schröder-Turk, G.E., Kapfer, S.C., Breidenbach, B., Beisbart, C. & Mecke, K. (2008): Tensorial Minkowski functionals and anisotropy measures for planar patterns. *J. Microsc.* **238**, 57-78.

Schröder-Turk, G.E., Mickel, W., Kapfer, S.C., Schaller, F.M., Breidenbach, B., Hug, D. & Mecke, K. (2010): Minkowski tensors of anisotropic structures. arxiv.org: 1009.2340.

Stelldinger, P. & Köthe, U. (2006): Connectivity preserving digitization of blurred binary images in 2D and 3D. *Computers & Graphics* **30**, 70 - 76.

Svane, A.M. (2012a): Local digital algorithms for estimating the integrated mean curvature of *r*-regular sets. *CSGB Research Reports* **12-08**. Submitted.

Svane, A.M. (2012b): Local digital estimators of intrinsic volumes for Boolen models and in the design based setting. *CSGB Research Reports* **12-07**. Submitted.

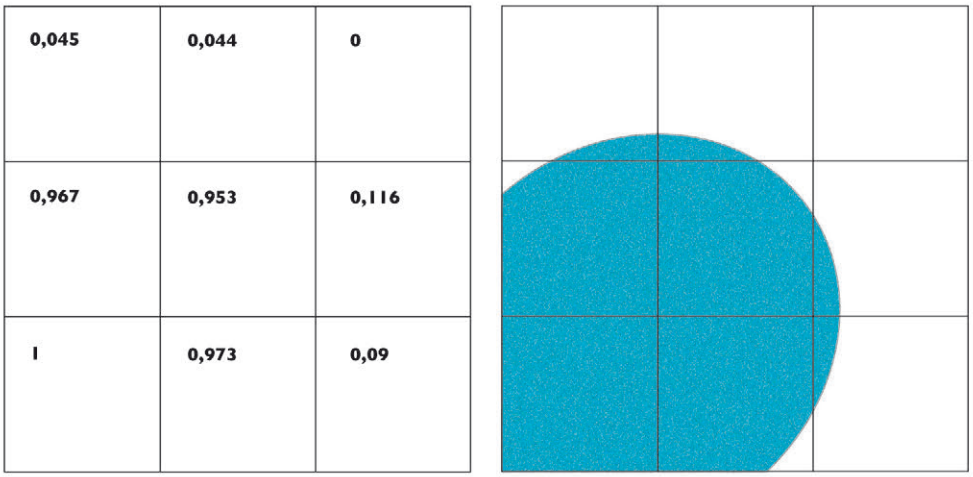


Figure 1: Illustration of the refined digital image of a planar set which associates to each lattice square, the areal fraction of the set inside the square (left). The original set is the blue set (right).

RESEARCH | INTEGRAL GEOMETRY AND ADVANCED STEREOLOGY

TOPOLOGY AND DIGITAL IMAGE ANALYSIS

The classical mathematical approach to 2D digital images is to furnish the Euclidean plane with a lattice L, for convenience evenly spaced, with grid-size d. For any subset X of the plane, the digital image of X with respect to L is simply $X \cap L$.

The **pixel approximation** $P(X \cap L)$ to X is the union of the squares of side-length d centered at the points of $X \cap L$ with sides parallel to the lattice directions of L. An alternative is the **cellular approximation** $C(X \cap L)$; this is the union of the squares of side d all of whose vertices lie in $X \cap L$.

Neither of these two approximations (nor in fact the one or two others that have been proposed) will in general correctly reconstruct even the topology of X; it turns out that reconstruction is likely to fail as soon as the boundary ∂X of X is not a continuously differentiable regular curve. On the other hand, if ∂X is a bounded continuously differentiable regular curve, then these approximations will correctly reconstruct the topology of X when d is sufficiently small.

In Pavlidas (1982), it has been proved that the pixel approximation and the cellular approximation of a regular object capture the topology when the resolution of the image is sufficiently fine. It has turned out to be much harder to reconstruct geometry. A central idea for our project is to consider the **refined digital image** which to each point p of the lattice associates the areal fraction of X inside a square of side centered at p.

Using the refined digital image, it is possible to reconstruct the topology more efficiently than in the case where either the pixel approximation or the cellular approximation is used.

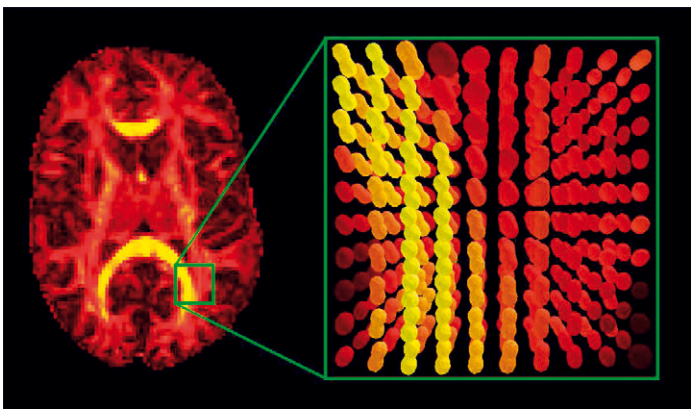
To reconstruct some geometry, results on the differential geometry of regular curves with bounded curvature can be used. For bounded and connected X, an algorithm has been established to determine quite precisely which sides of which lattice squares, the boundary curve ∂X must cross.

The approach produces visually satisfying approximations X' to X in practice. To see that this construction can be made in general, and algorithmically, in such a way that the boundary of X' approximates the boundary of X, also in terms of arc-length and curvature, and in such a way that the approximation improves, as the side length in the lattice goes to zero, are the next aims of the project.

Diffusion MRI

In a collaborative project between AU-math and KU, diffusion MRI images of the brain are studied with the aim of extracting information about brain connectivity. These images encode at each voxel the probability of diffusion in a number of directions, indicating the local direction of brain fibres, but suffer from a low signal-to-noise ratio, that strongly affects brain fibre reconstruction. In this subproject, these problems are addressed on two fronts: firstly, by improving the image reconstruction methods via numerical geometrical methods, and secondly, by using graph kernel methods on connectivity graphs extracted directly from the images rather than depending on preprocessing such as fibre tracking.

This project is inspired by an earlier project performed at AU-math in collaboration with Centre of Functionally Integrative Neuroscience, see Frandsen *et al.* (2007). The data typically involved in diffusion MRI is illustrated below.



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References

Frandsen, J., Hobolth, A., Østergaard, L., Vestergaard-Poulsen, P. & Jensen, E.B.V. (2007): Bayesian regularization of diffusion tensor images. *Biostatistics* **8**, 784-799.

Pavlidas, T. (1982): *Algorithms for Graphics and Image Processing*. Computer Science Press.

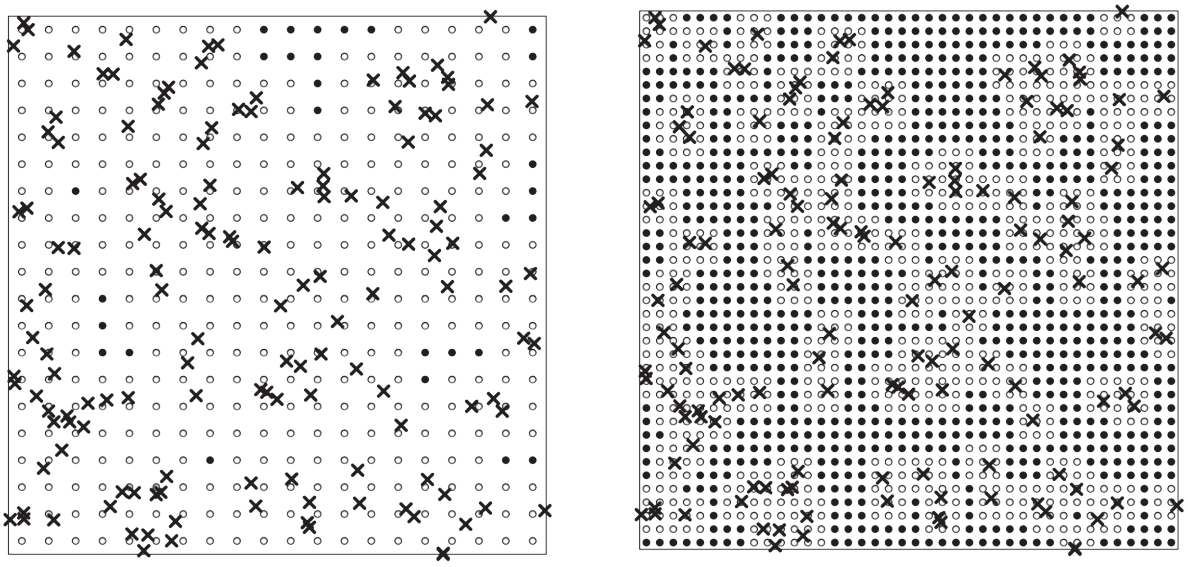


Figure 1: From Coeurjolly & Møller (2012) where a new variational approch to estimation of the intensity of a spatial point process is developed.

RESEARCH | STATISTICS OF STOCHASTIC GEOMETRY MODELS

SPATIAL AND SPATIO-TEMPORAL POINT PROCESSES

During 2012, the research on spatial and spatio-temporal point processes has mainly been focused on (1) development of a fast method of estimating the innovation covariance for spatial Gibbs point processes, (2) a study of the statistical properties of determinantal point processes and (3) development of a new variational approach to point process intensity estimation. Below, the main results are summarized.

In collaboration with Jean-François Coeurjolly, University of Grenoble, an exact formula for the covariance of two **innovations** computed for a spatial **Gibbs point process** has been derived (Coeurjolly & Rubak, 2012). A fast method of estimating the innovation covariance has been developed. This methodology has been used to estimate the asymptotic covariance matrix of the maximum pseudo-likelihood estimate of the parameters of a spatial Gibbs point process model. This allows for the construction of **asymptotic confidence intervals** for the parameters. The efficiency of the procedure is illustrated in a simulation study involving several classical parametric models. – It is part of the future research plans also to consider, in collaboration with Adrian Baddeley, University of Western Australia, an alternative estimation method for Gibbs point processes based on logistic regression.

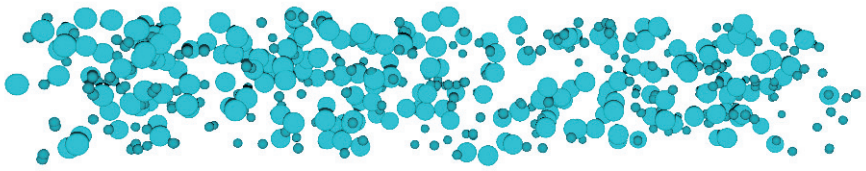
Permanental and **determinantal point processes** have a likelihood expressed in terms of weighted permanents respective determinants. In Lavancier *et al.* (2012), the statistical properties of determinantal point processes, which form the most promising and tractable class of permanental and determinantal point processes, are studied. Determinantal point processes (DPPs) are useful models for **repulsiveness**. For stationary DPPs, a simple condition is given in Lavancier *et al.* (2012) that ensures their existence, and

it is described how the models can be well approximated so that the likelihood can be evaluated and realizations simulated. - The research on DPPs will be continued. The properties of a DPP is determined solely by its covariance function. The possibilities and limitations of DPPs in statistical applications will be investigated by analyzing covariance functions through their associated integral operators and representation in function spaces known from mathematical analysis.

In Coeurjolly & Møller (2012), a new variational estimator for the intensity function of an inhomogeneous spatial point process is introduced. The **variational estimator** applies when the intensity is of log-linear form. Its strong consistency and asymptotic normality is established and its finite-sample properties is discussed in comparison with the maximum first order composite likelihood estimator, when considering various spatial point process models.

As part of our future research plans, the use of spatial point processes in magnetic resonance imaging (MRI) will also be investigated. More specifically, we wish to find ways of predicting the quality of the final images before reconstruction, by transforming the observed spatial frequencies into spatial point patterns reflecting the final geometry of the image.

Finally, the papers Møller & Berthelsen (2012), Møller & Ghorbani (2012) and Møller & Rasmussen (2012) have appeared during 2012.



Minicolumn project

Various statistical methods for testing the existence of minicolumns in three-dimensional point pattern datasets consisting of cell centers have been tried. The methods include the use of classical summary statistics used for analyzing point processes (such as Ripley's *K*-function), and newly developed methods specifically designed for discerning minicolumns. The new methods are based on nearest neighbour relationships, anisotropic summary statistics, and Delaunay tessellations. So far none of the approaches have shown the existence of minicolumns, but some differences have been observed between the data and simulations of a homogeneous Poisson process. - As a next step in the minicolumn project, we plan to analyze data not only containing cell centers, but also the orientation and shape of the cells.

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References

Coeurjolly, J.-F. & Møller, J. (2012): Variational approach for spatial point process intensity estimation. *CSGB Research Reports* **12-09**. Accepted for publication in *Scand. J. Statist.*

Coeurjolly, J.-F. & Rubak, E. (2012): Fast covariance estimation for innovations computed from a spatial Gibbs point process. *CSGB Research Reports* **12-03**. Accepted for publication in *Scand, J. Statist.*

Lavancier, F., Møller, J. & Rubak, E. (2012): Statistical aspects of determinantal point processes. *CSGB Research Reports* **12-04**. Submitted.

Møller, J. & Berthelsen, K.K. (2012): Transforming spatial point processes into Poisson processes using random superposition. *Adv. Appl. Probab.* **44**, 42-64.

Møller, J. & Ghorbani, M. (2012): Aspects of second-order analysis of structured inhomogeneous spatio-temporal point processes. *Statistica Neerlandica* **66**, 472-491.

Møller, J. & Rasmussen, J.G. (2012): A sequential point process model and Bayesian inference for spatial point patterns with linear structures. *Scand. J. Statist.* **39**, 618-634.

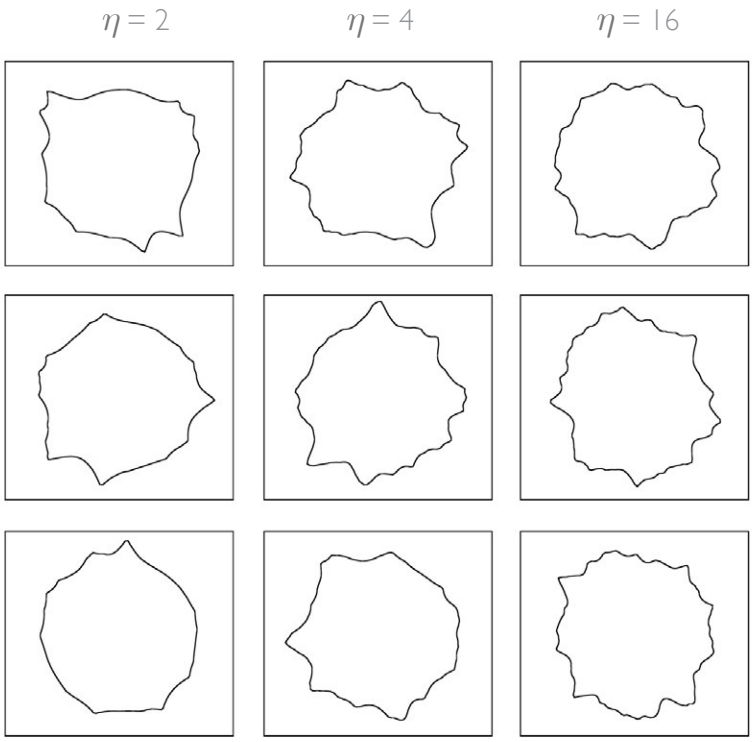

Figure 1:
Realizations of particles obtained by assuming that the squared radial function is given by a Gamma Lévy process with a second-order covariance function. Each column corresponds to realizations for a fixed value of η, determining the distribution of the Gamma Lévy basis. From Jónsdottir & Jensen (2012).

RESEARCH | STATISTICS OF STOCHASTIC GEOMETRY MODELS

SPACE-TIME LATTICE DATA

This project concerns statistical inference for space-time lattice data with emphasis on data generated in important bioimaging applications, where typically the sites of the lattice corresponds to pixels or voxels in a 2D or 3D image.

A major focus point in this project is the development of statistical inference procedures for **Lévy based random fields**. Such random fields constitute a flexible model class, based on kernel smoothing of a so-called Lévy basis. The resulting fields may be Gaussian, but there are many other possibilities, e.g. random fields based on Gamma, inverse Gaussian and normal inverse Gaussian (NIG) Lévy bases.

Modelling the distributional properties of the random field under consideration may actually be very important. For instance, in brain imaging, a widely used procedure for testing the hypothesis of no difference between two groups of subjects is to calculate a *t*-test statistic of no difference between the groups at each voxel and declare a voxel as significant if the observed value of the *t*-test statistic in the voxel exceeds the 95 percentile in the **distribution of the maximal test statistic** under the null hypothesis. Such a procedure is very sensitive to the distributional assumptions of the underlying random field.

In 2012, Lévy based modelling has been the focus in Jónsdóttir & Jensen (2012) where the Lévy approach has been used in error prediction in circular systematic sampling. The special case of a Gaussian basis has been considered in Hansen & Thorarinsdottir (2012) where the fractal properties of the resulting moving average Gaussian random field are studied.

Apart from Lévy based modelling, modelling of FRET data which can be described as a multivariate random field, has been studied in 2012. For further details, see the section **Fluorescence microscopy taken to the molecular level**.

There are still a number of unsolved issues relating to **statistical inference procedures** for Lévy based random fields. To fix ideas, a Lévy based random field $X = \{X_v : v \in R^d\}$ is defined via the following stochastic integral

$$X_v = \int_{R^d} k(u - v)Z(\mathrm{d}u), \quad v \in R^d,$$

where k is a kernel function and Z is a homogeneous and factorizable Lévy basis.

The most common estimation method is a **two-step procedure**, where first the kernel function k is estimated by fitting a parametric variogram model to its empirical counterpart and then estimates of the parameters determining the distribution of Z are obtained by using moment estimation, which is natural as the theoretical cumulants are easily obtainable.

There are various possibilities for improving the existing procedure for parameter estimation. The estimation of the kernel function requires that a suggested parametric variogram model is compatible with the observed empirical variogram and that there is a simple one-to-one relationship between the **variogram model** and the kernel function. When the empirical variogram is not compatible to known parametric variogram models, an alternative is to consider a non-parametric estimation of the kernel function based on **Fourier inversion**.

One drawback of the method of moments for estimating the underlying distribution is that the observed data is correlated, which results in biased estimates of the moments and/or cumulants. It is therefore needed to derive correction formulas for the empirical moments and cumulants of correlated data, which can be used for improving the moment estimation. A more computionally demanding estimation method is **pseudo maximum likelihood estimation**. There are different methods for approximating the marginal density of X_v for establishing a pseudo likelihood function. The simplest form of approximation is to approximate the marginal distribution of X_v by a distribution from the same parametric family as the distribution of the underlying Lévy basis. A more complicated approximation is a **saddlepoint approximation**.

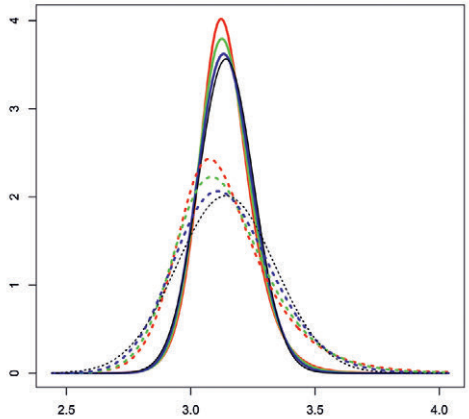

Figure 2:
Saddlepoint densities of the area estimator based on measurement of the radial function in n systematic directions, where $n = 5$ (stippled) and $n = 10$ (full line). The different colours represent densities for the three particles considered: $\eta = 2$ (red lines), $\eta = 4$ (green lines) and $\eta = 16$ (blue lines). Densities for a Gaussian model is shown for comparison (black lines). From Jónsdóttir & Jensen (2012).

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References

Hansen, L.V. & Thorarinsdottir, T.L. (2012): A note on moving average models for Gaussian random fields. *CSGB Research Reports* **12-13**. Submitted.

Jónsdóttir, K.Y. & Jensen, E.B.V. (2012): Lévy based modelling in circular systematic sampling. *CSGB Research Reports* **12-10**. Submitted.

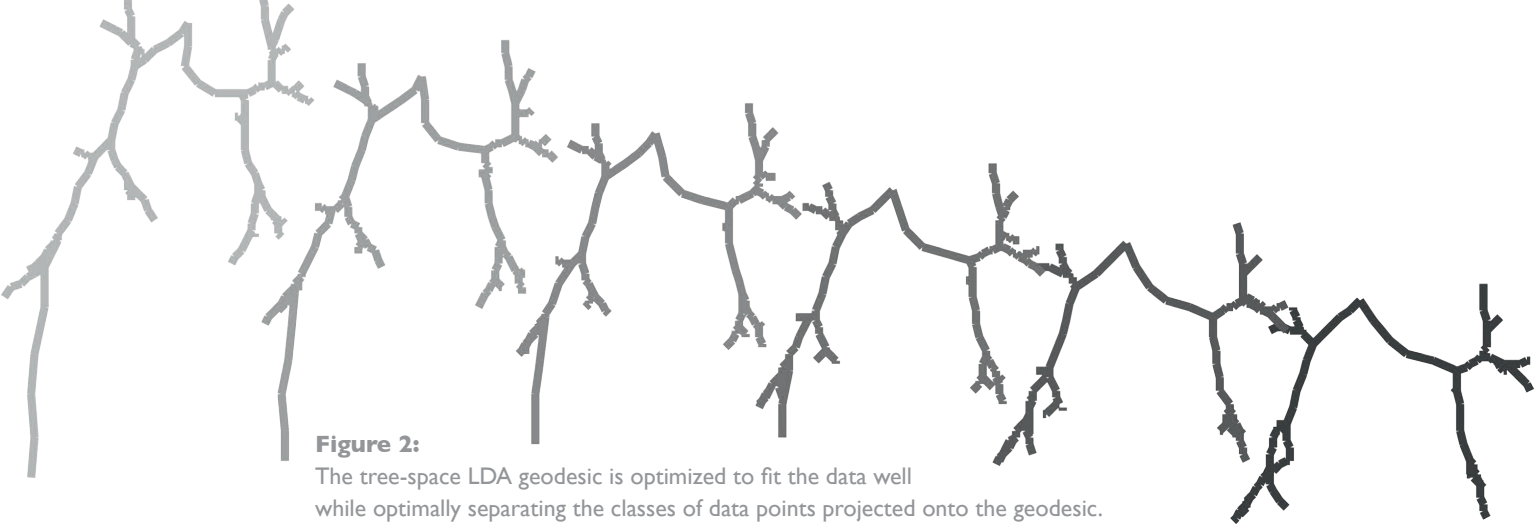

Figure 2:
The tree-space LDA geodesic is optimized to fit the data well while optimally separating the classes of data points projected onto the geodesic. From Feragen *et al.* (2013b).

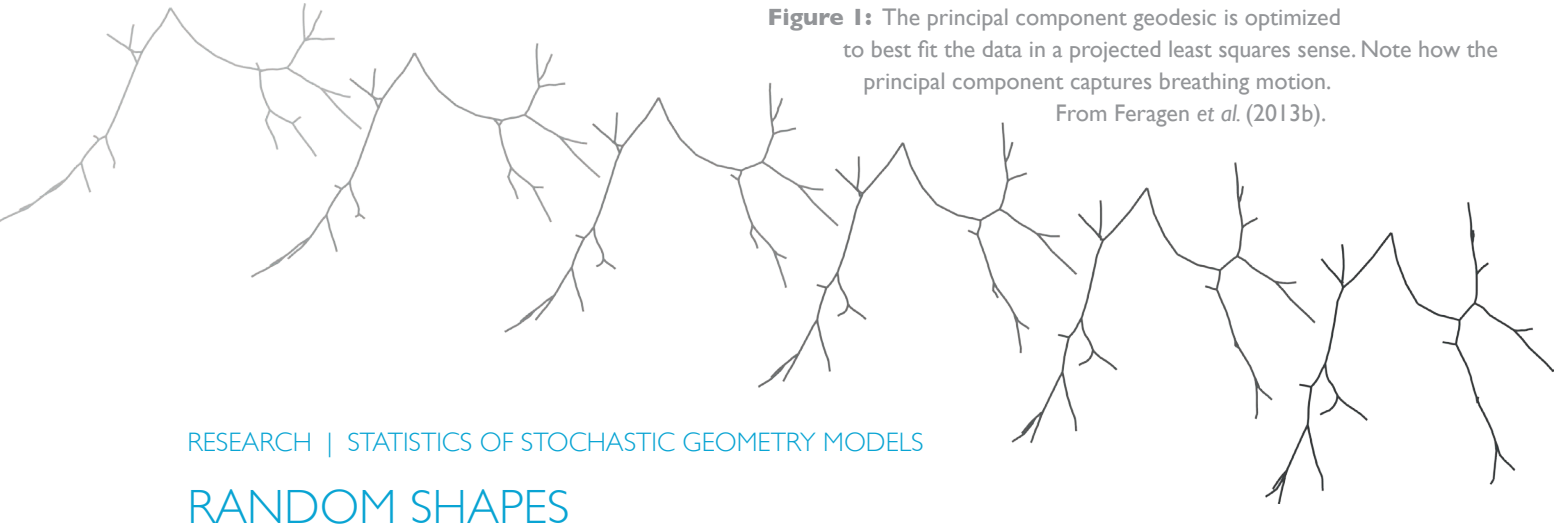

Figure 1: The principal component geodesic is optimized to best fit the data in a projected least squares sense. Note how the principal component captures breathing motion. From Feragen *et al.* (2013b).

RESEARCH | STATISTICS OF STOCHASTIC GEOMETRY MODELS

RANDOM SHAPES

In this project, different types of random shapes are studied. Initially, the focus was on planar curves, represented by labeled points with some equidistance relations, called Bicycle Chain Shape models. This has led us to the development of general tools for performing and understanding statistics in Riemannian manifolds (Sommer *et al.*, 2012a). As **3D images** are now routinely produced in medical and biological imaging, the focus has during the project period gradually changed from 2D to 3D shapes. Since point distribution models for 2D shapes do not generalize that easily to models in 3D for surfaces and volumes, we have instead studied the Large Deformation Diffeomorphic Metric Mapping **(LDDMM)** and some extensions of it to multi-scale and sparse and more compact representations, see Sommer *et al.* (2012b, c; 2013) and references therein. The work based on the LDDMM approach will be continued, especially the part relating to brain registration and numerical methods for regression and interpolation on shape manifolds.

Geometric trees form an important class of shapes, which appear as anatomical networks such as blood vessels, dendrite trees or airway trees from lungs. The analysis of structured data like anatomical trees is an emerging field in mathematical statistics, geometric data analysis and image analysis. We are particularly interested in the shape of airway trees from lungs, which are an instance of unordered, unlabeled geometric trees. In Feragen *et al.* (2013a), a general geometric framework is developed for analyzing such trees in a geodesic space of trees. It turns out that in this space of very general trees, the problem of computing geodesics between trees is NP complete (Feragen, 2012). By constraining to labelled trees, geodesics can be computed in polynomial time (Owen & Provan, 2011). We have proposed an airway tree

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labeling algorithm (Feragen *et al.*, 2012) which uses geodesic distances between labeled trees to evaluate suggested labelings. This algorithm is accurate and reproducible, and sufficiently efficient to label a whole medical database of roughly 10.000 airway trees (Feragen *et al.*, 2012; Petersen *et al.*, 2012a, b). We next developed methods to compute properties such as mean tree, principal component, hypothesis tests or most discriminative geodesic in the spirit of linear discriminant analysis (Feragen *et al.*, 2013b), results which in particular give us useful new methods to visualize the data variation in tree-space (Figure 1) as well as insight into class variance (Figure 2).

The research on analysis of geometric trees will be continued. This includes development of kernel methods for geometric trees and graphs. Through kernels for geometric graphs, we will also start to analyze brain connectivity extracted from medical images. See the subsection on Diffusion MRI in the section on **Topology and Digital Image Analysis**.

References

Feragen, A. (2012): Complexity of computing distances between geometric trees. *International Workshop on Structural and Syntactical Pattern Recognition (SSPR)*, 11pp.

Feragen, A., Lo, P., de Bruijne, M., Nielsen, M. & Lauze, F. (2013a): Towards a theory of statistical tree-shape analysis. *Transactions of Pattern Analysis and Machine Intelligence (TPAMI)*, in press.

Feragen, A., Owen, M., Petersen, J., Wille, M.M.W., Thomsen, L.H., Dirksen, A. & de Bruijne, M. (2013b): *23rd biennial International Conference on Information Processing in Medical Imaging (IPMI 2013)*, in press.

Feragen, A., Petersen, J., Owen, M., Lo, P., Hohwu, L., Wille, M., Dirksen, A. & de Bruijne, M. (2012): A hierarchical scheme for geodesic anatomical labeling of airway trees. *Proceedings of MICCAI 2012*, 147-155.

Owen, M. & Provan, S. (2011): A fast algorithm for computing geodesic distances in tree space. *IEEE/ACM Transactions on Computational Biology and Bioinformatics* **8**, 2-13.

Petersen, J., Feragen, A., Owen, M., Wille, M.M.W., Thomsen, L.H., Dirksen, A. & de Bruijne M. (2012a): Automatic system for segmentation, longitudinal matching, anatomical labeling and measurements of airways from CT image. Extended abstract, *IMAGINE workshop, European Congress of Radiology 2012*.

Petersen, J., Feragen, A., Thomsen, L.H., Wille, M.M.W., Dirksen, A. & de Bruijne, M. (2012b): Manual airway labeling has limited reproducibility. *European Congress of Radiology 2012*.

Sommer, S.H., Lauze, F.B. & Nielsen, M. (2012a): The differential of the exponential map, Jacobi fields and exact principal geodesic analysis. Submitted.

Sommer, S.H., Lauze, F., Nielsen, M. & Pennec, X. (2012b): Kernel bundle EPDiff: evolution equations for multi-scale diffeomorphic image registration. *Proceedings of the Third International Conference on Scale Space and Variational Methods in Computer Vision*, 677-688.

Sommer, S.H., Nielsen, M. & Pennec, X. (2012c): Sparsity and scale: compact representations of deformation for diffeomorphic registration. MMBIA Workshop at WACV 2012, Breckenridge, Colorado.

Sommer, S.H., Nielsen, M., Darkner, S. & Pennec, X. (2013): Higher-order momentum distributions and locally affine LDDMM registration. *SIAM Journal on Imaging Sciences* **6**, 341-367.

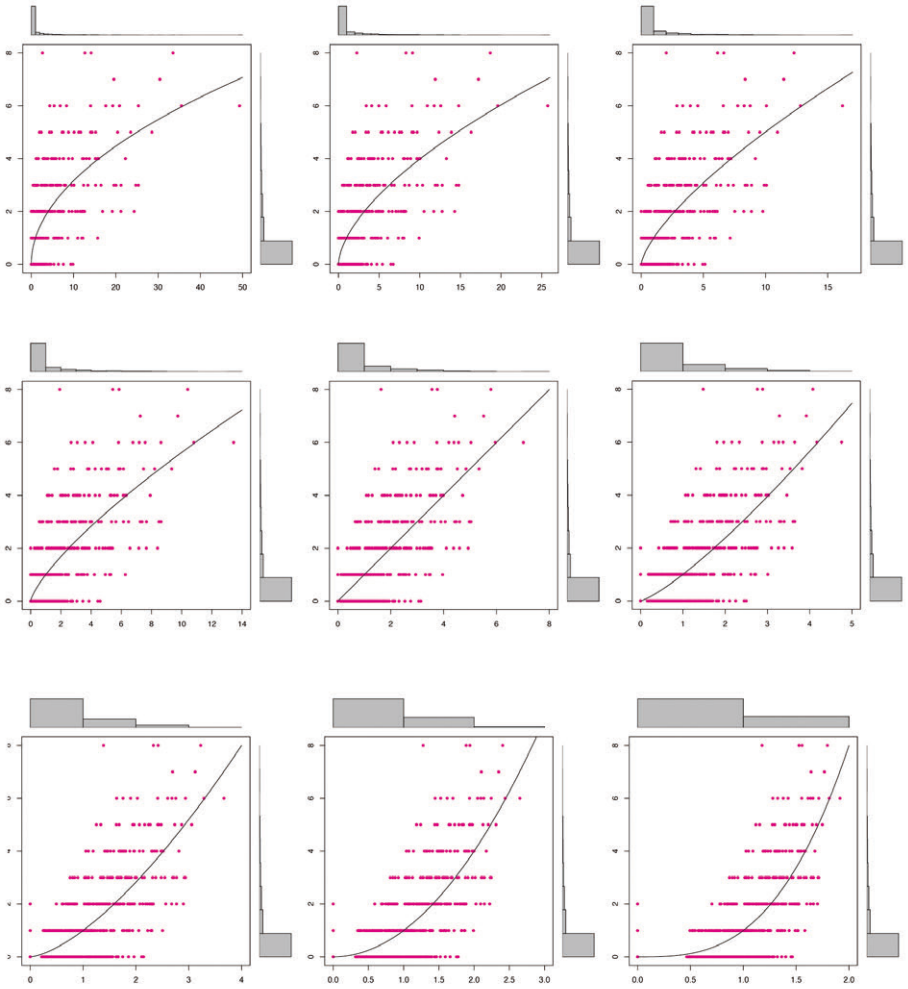

Figure 1:
Scatterplot of the joint distribution of (x_j, N_j) used in one of the simulation studies. The fraction of FOVs with vanishing auxiliary variables is 0.05. In stratum 1 (non-vanishing auxiliary variables), the marginal distribution of x_j is a scaled and translated Beta distribution, while the conditional distribution of N_j given x_j is Poisson with parameter proportional to x_j^{δ} where δ = 0.5, 0.6, 0.7, 0.75, 1, 1.25, 1.5, 2, 3 (from top left to bottom right). The mean value of N_j as a function of x_j is shown on each plot as a solid curve. The marginal distributions of x_j and N_j are also indicated on the plots.

RESEARCH | ADVANCED BIOIMAGING

NON-UNIFORM SAMPLING

Non-uniform sampling of anisotropic or inhomogeneous structures has considerable practical interest in microscopy. At the moment, the principle has been put forward in the applied litterature, and it has been shown that important reductions in estimator variances may be obtained by using non-uniform sampling compared to traditional systematic uniform sampling.

Probably the most common application of non-uniform sampling in microscopy so far is the so-called proportionator (Gardi *et al.*, 2008), which is a special type of pps sampling with an auxiliary variable x_j obtained as the grey or color value of the the jth field of view measured on a low resolution digital image. Associated with the jth field of view is also the number N_j of cells in the window. This number are only observable at a high magnification. The aim is to estimate the total number of cells.

Since pps sampling in connection with the Horvitz-Thompson estimator requires that all $x_j > 0$, it was suggested in Gardi *et al.* (2008) to use $x_j + \varepsilon$ as measure of size, where ε takes some small prechosen value. In order to get an impression of the relation between the auxiliary variable x_j and the number N_j of cells in a concrete example, an extensive study (Keller *et al.*, 2012) has been carried out in 2012 at AU-bio. It turned out that about 5% of the cells were found in fields with $x_j = 0$. Together with the small "extra weight" ε as suggested by the current software, this leads to extremely high variances.

Vanishing auxiliary variables

One way of dealing with vanishing auxiliary variables is to partition the population into two strata, a "stratum 0" consisting of fields of view with $x_j = 0$, and a stratum with $x_j > 0$ ("stratum 1"). Subsequently, pps sampling is only applied to stratum 1, while stratum 0 is sampled with uniform probability. The estimate of the total number of cells is then obtained as the sum of the two estimates in the separate strata. In 2012, we have studied model-assisted approaches to optimal allocation of the sample to the two strata. This allocation depends on parameters of the model, that may be determined by a pilot study. The robustness of the model-assisted approach towards deviations of the assumed parameters, and towards model misspecification, has been investigated by simulation.

Variance of the proportionator

The proportionator combines the variance reduction idea of pps sampling with a particular systematic sampling scheme, the so-called smooth fractionator (Gundersen, 2002). This may lead to further variance reduction, but also makes it impossible to use traditional variance estimators known from sampling theory. In order to understand the consequences of this particular sampling scheme, we have translated it into the language of sampling theory, and compared it to other existing sampling schemes that allow for variance estimation. Due to the complexity of proportionator sampling, it has not been possible to derive theoretical results, and we have resorted to simulation studies. We have identified appropriate and flexible models for the population, consisting of pairs (x_j, N_j), by comparison with the experimental data that has been collected at AU-bio.

In collaboration with Johanna F. Ziegel (Bern), the possibility of using bootstrap methods for variance estimation has been explored.

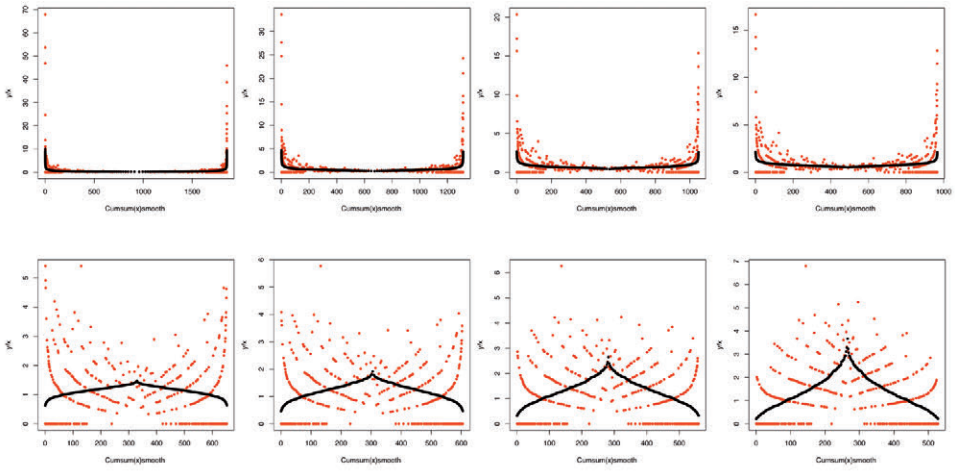

Figure 2:
Scatterplot of the joint distribution of $(x_j, N_j / x_j)$ ordered such that the auxiliary variable x_j is balanced (proportionator sampling). The mean curves are also shown. The values of δ are 0.5, 0.6, 0.7, 0.75, 1.25, 1.5, 2, 3 (from top left to bottom right).

Researchers

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Ina Trolle Andersen
Ute Hahn
Jens R. Nyengaard
Johanna F. Ziegel

References

Gardi, J.E., Nyengaard, J.R. & Gundersen, H.J.G. (2008): Automatic sampling for unbiased and efficient stereological estimation using the proportionator in biological studies. *J. Microsc.* **230**, 108-120.

Gundersen, H.J.G. (2002): The smooth fractionator. *J. Microsc.* **207**, 191-210.

Keller, K.K., Andersen, I.T., Andersen, J.B., Hahn, U., Stengaard-Pedersen, K., Hauge, E.-M. & Nyengaard, J.R. (2012): Improving efficiency in stereology: A study applying the proportionator and the autodisector on virtual sections. Submitted.

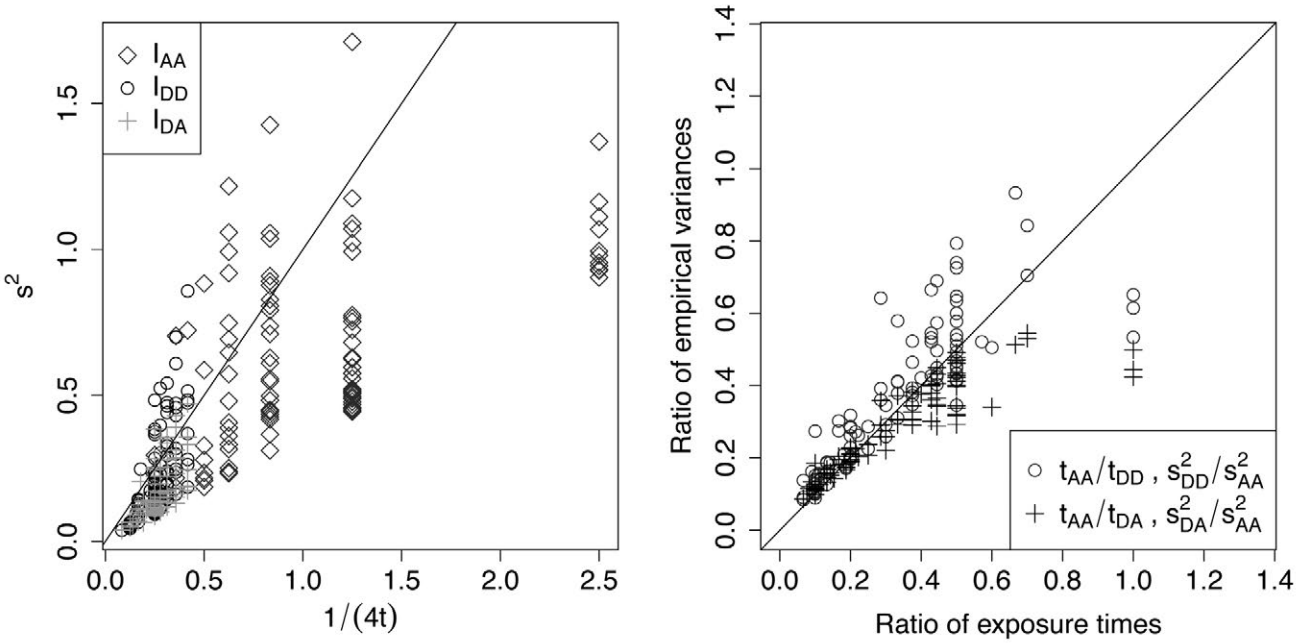

Figure 1:
Comparison of inverse exposure times and the empirical variance (estimated from the pixel variation within an image). Left: Direct comparison of empirical noise variance (ordinate) and 1/(4*t*) expected under Poisson variation (abscissa). Right: Comparison of ratios of empirical variances and ratios of exposure times. From Jensen *et al.* (2012).

RESEARCH | ADVANCED BIOIMAGING

FLUORESCENCE MICROCOPY TAKEN TO THE MOLECULAR LEVEL

Fluorescence microscopy data provide information about the cell membrane organization and dynamics of receptors which are playing a major role in neuronal processes relating to the development of neurodegenerative and depressive disorders. Our efforts in 2012 have been concentrated on the collection and analysis of data obtained by Förster resonance transfer (FRET) microscopy by means of the sensitized acceptor emission approach which is relying on the collection of triplets of images for donor- and acceptor-labeled cellular samples. The problem has been attacked in two different ways as described in more detail below.

K_d and E_m estimation

In FRET microscopy, three images are observed for each cell. A complete dataset typically consists of a few hundred of such image triplets. In Chen *et al.* (2007), a first approach to estimating K_d and E_m based on the three images has been presented. The so-called **dissociation constant K_d** is a measure of the average protein-protein interaction strength, while the **FRET efficiency E_m** is a measure of the average donor-acceptor distance. The method used in Chen *et al.* (2007) assumes no noise in two of the images and for each cell the three images are reduced to three average pixel intensities. The dataset is thereby reduced to a few hundred triplets of pixel averages. This reduction is based on the fundamental assumption of biology that the values of K_d and E_m are constant within a cell as well as for a population of cells. As an alternative to this method, we have developed a probability model on the pixel level which includes measurement noise in all three images. We use a **total least squares method**

in the parameter estimation, based on the millions of pixel values constituting a cellular image rather than the reduced dataset of averages. This pixel-based approach has allowed us to estimate parameters for individual cells whereas the method based on averages yields a single estimate for all cells. A reanalysis of the Chen *et al.* data by the new method has shown a considerable variability in the individual estimates of between cells as well as intracellularly that cannot be explained by the **measurement noise** (Jensen *et al.*, 2012); this is very interesting news that we are currently investigating further. One of the next steps is to develop statistical tests for the hypothesis that the FRET efficiency is significantly different from zero.

CELLULAR PROTEIN INTERACTIONS AND SPATIAL POINT PROCESS MODELS

We have initiated the development of spatial point process models for the distribution of proteins throughout living cells and a study of a physical model (Corry *et al.*, 2005) for the generation of FRET pixel intensity data given a protein configuration. The idea is to combine the two models in order to obtain a **complete stochastic model** for the generation of FRET pixel intensity data. This combined model is quite challenging from a computational point of view and we consider various approximations that simplify computations drastically without serious implications regarding accuracy. Based on the approximated combined model we are developing **Markov chain Monte Carlo algorithms** for Bayesian inference regarding parameters in the spatial point process model.

This will allow us to draw quantitative statements concerning the protein arrangement at an inner pixel level. Subsequently, we want to use this approach in a study of the interaction of a particular receptor-receptor pair, Sortilin and p75, in the plasma membrane of living cells. The experimental dataset will be provided by AU-bio. This will require experimental optimization of the cellular expression of p75 and Sortilin which is currently in progress.

Different methods for statistical inference of protein interaction data have been discussed in the literature, including the methods of moments, full Bayesian inference and approximate Bayesian inference (Turner & Zandt, 2012). The performance of these methods will be compared on 'clean' FRET data sets.

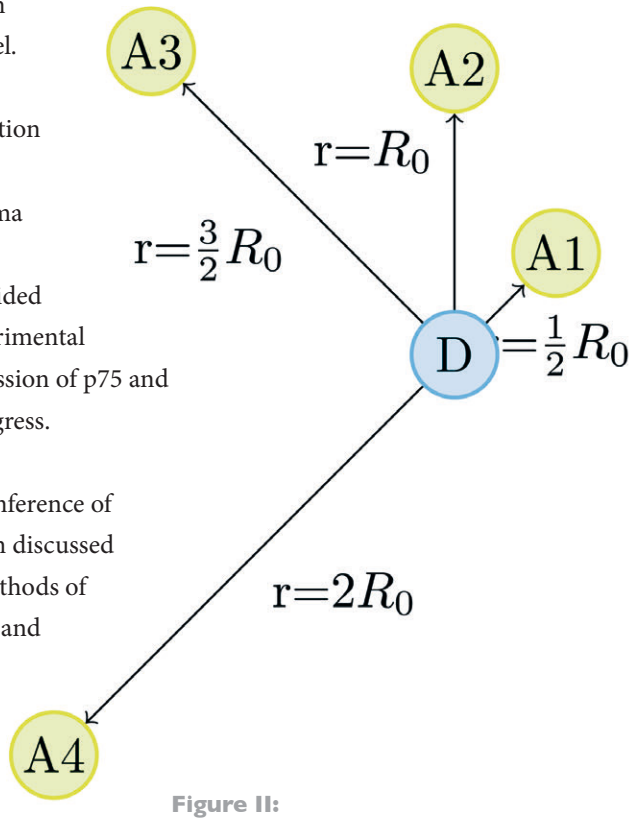

Figure II:
Multiple-acceptors surrounding a donor.

Researchers

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Jens Ledet Jensen
Jens R. Nyengaard
Merete Raarup
Ege Rubak
Rasmus P. Waagepetersen

References

Chen, H., Puhl, H.L. & Ikeda, S. R. (2007): Estimating protein-protein interaction affinity in living cells, using quantitative Förster resonance energy transfer measurements. *J. Biomed. Opt.* **12**, 054011.

Corry, B., Jayatilaka, D. & Rigby, P. (2005): A flexible approach to the calculation of resonance energy transfer efficiency between multiple donors and acceptors in complex geometries. *Biophys. J.* **89**, 3822-3836.

Jensen, J.L., Raarup, M.K. & Rubak, E. (2012): Estimating protein-protein interaction affinity from single living cells. *CSGB Research Reports* **12-12**. Submitted.

Turner, B. & Zandt, T.V. (2012): A tutorial on approximate Bayesian computation. *J. Math. Psychol.* **56**, 69-85.

A

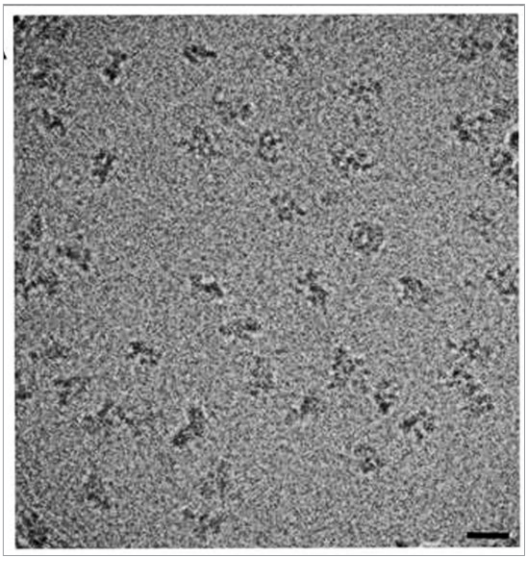


Figure 1A:
Cryo-EM image of the prokaryotic small 30S ribosomal subunit. The small ribosomal subunit is a relatively slim particle consisting of a 16S RNA molecule and 21 proteins.

B

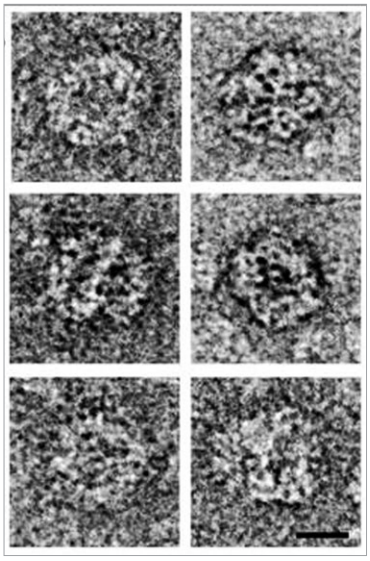


Figure 1B:
Negatively stained images of pyruvate dehydrogenase complexes from the yeast Saccharomyces cerevisiae (scale bar: 20 nm).

MOLECULAR CRYO-EM

In molecular cryo-EM, we aim at studying the three-dimensional (3D) structure of **macromolecular complexes** purified from cells. Structure determination in cryo-EM represents a multi-disciplinary challenge that among other things includes the development of purification strategies yielding pure complexes from cells as well as the imaging process in the electron microscope. Finally, the images have to be processed computationally in order to determine 3D models from the images.

Cryogenic conditions (~-180˚C) reduce damage of the beam-sensitive material and enable **imaging of frozen samples** under native hydrous conditions despite the high vacuum in the microscope. The underlying concept of 3D cryo-EM implies that a purified macromolecular sample consists of millions of identical copies of a single structural design of which **projection images** are retrieved in different orientations. Most macromolecular complexes, however, have been shown not easily to follow this concept in a straightforward way, as they naturally exist as sets of structurally related, but distinguishable objects due to compositional or **conformational heterogeneity**. The general approach to deal with this 'biological imperfection' is to identify sub-groups of particles within a large data set, in which the original assumption is met, at least within the limitations of the technically achievable resolution, and to determine separate 3D structures for these groups. This approach should furthermore include techniques and criteria to identify and exclude particles which due to technical reasons do not fit into any group, as these particles would merely increase the background noise and lower the resolution.

The development of techniques to deal with naturally occurring structural variation within a given sample is of high relevance for the understanding of protein-protein interactions in health and disease. Importantly, it is mostly the **function-related dynamics** of a particle that constitutes the causative origin of structural heterogeneity in cryo-EM images. Typical examples comprise structural changes during progression through a catalytic cycle, interaction with molecular partners or modification by other enzymes. In these cases, the specimen represents a frozen snapshot of the particle as a starting point to understand its dynamics.

Here, we aim at identifying, purifying and imaging macromolecular complexes which can serve as model particles to study and understand structural heterogeneity and to deal with it computationally. To this end, we purified small (30S) subunits of the **prokaryotic ribosome** (Fig. 1A). The small ribosomal subunit is a relatively slim particle consisting of a 16S RNA molecule and 21 proteins. During ribosomal protein translation, the 30S subunit exhibits a considerable amount of structural dynamics that represents a challenge for studies by cryo-EM. In solution, different conformers are adopted randomly, a fact that makes the small subunit an advantageous particle for the study and development of sorting and 3D reconstruction algorithms for conformationally heterogeneous samples.

The second particle followed is the **pyruvate dehydrogenase complex** (PDH) from Baker's yeast Saccharomyces cerevisiae, a protein complex difficult to purify for cryo-EM under native conditions. PDH forms a dodecahedral core structure to which regulatory proteins can transiently attach in order to control its activity. Thus, PDH represents a model system suitable for studying sorting procedures as well as algorithms that deal with heterogeneity to improve the attainable resolution. We have genetically tagged a main core subunit with a **One-STrEP affinity purification tag**, and we also affinity-tagged the regulatory proteins. The correct integration of the tags into the genome of the different yeast strains could be confirmed by PCR followed by sequencing. We continued with small-scale biochemical purification experiments which confirmed that the protein of interest is obtained, and could also image the corresponding macromolecular complexes under negatively-stained, room temperature conditions as a prerequisite for future studies under cryogenic conditions (Fig. 1B).

Reconstruction algorithms in cryo-EM

From the computational side, we work on two main problems:

- to determine the angular relationship between the individual projection views
- to solve the ill-posed reconstruction problem

We use Bayesian statistical inversion in both problems to optimally cope with the high amount of noise, as well as to incorporate prior structural information into the reconstruction problem. In one approach, we investigate the statistical recovery of the common line geometry between a set of projection images. The common line geometry describes the uncalibrated, affine projection geometry of two views that can be estimated without establishing pointwise correspondences between the views. The basic 2-view algorithm was described in Brandt *et al.* (2012) and we are currently working on the N-view extended approach. This method will ultimately be combined with another approach, where we study the actual reconstruction problem. In this work, we find the maximum à posteriori (MAP) estimates for the particle structure from the marginal posterior, where the view orientations are integrated out. We aim at a statistically optimal result using a uniform prior in the space of particle rotations, see also Brandt *et al.* (2013). We are currently improving the projection model and studying advanced structural prior distributions. We also investigate efficient algorithms for reducing the computational complexity, allowing for a more complex subdivision of the reconstruction into different shape conformities.

Researchers

Monika Golas
Jay Rai
Björn Sander

Subproject Reconstruction algorithms
Sami Brandt
Katrine Hommelhoff Jensen
François Lauze

References

Brandt, S.S., Jensen, K.H. & Lauze, F.B. (2012): Bayesian epipolar geometry estimation from tomographic projections. *11th Asian Conference on Computer Vision, South Korea.*

Brandt, S.S., Jensen, K.H. & Lauze, F.B. (2013): On the Bayesian reconstruction method for randomly oriented particles in cryo-EM. *International Symposium on Biomedical Imaging, San Fransisco, CA. To appear.*

CENTRE ACTIVITIES

OVERVIEW - PAST AND PLANNED INTERNATIONAL ACTIVITIES

International conferences and workshops

- *Workshop on Quantitative Microscopy,* 20 – 27 August 2012, Bern
- *Workshop on Geometry and Statistics in Bioimaging: Manifolds and Stratified Spaces,* 8 - 12 October 2012, Sandbjerg
- *Joint EMS-DMF Mathematical Weekend,* 5 – 7 April 2013, Aarhus
- *Fourth Workshop on Geometry and Physics of Spatial Random Systems,* 8 – 10 April 2013, Aarhus

International minisymposia

- *Minisymposium on Convexity and Geometric Tomography*, 7 June 2012, Aarhus
- *Minisymposium on the occasion of the Midterm Evaluation of CSGB*, 13 October 2012, Aarhus

International PhD courses

- *Applied Nonsmooth Analysis and Multilevel Methods*, 30 January – 3 February 2012, Copenhagen
- *Introduction to Spatial Point Processes*, 11 - 13 June 2012, Aalborg
- *Summer school on Registration in Image Analysis and Computer Graphics*, 5 - 8 June 2012, Fasterbo, Sweden
- *Summer school on Domain Adaption Theory and Applications*, 20 - 24 August 2012, Copenhagen
- *Stereology Course*, 25 – 27 September 2012, Sandbjerg
- *Courses on Quantitative Medical Graphics*, 14 and 21 March, 31 October and 7 November 2012, Aarhus
- *Summer school on Topics in Space-Time Modelling and Inference*, 27 - 31 May 2013, Aalborg



Minisymposium, 7 June 2012
On 7 June 2012, a minisymposium on *Convexity and Geometric Tomography* was held at Department of Mathematics, Aarhus University. The invited speakers were (left) Richard Gardner (Western Washington University), (middle) Wolfgang Weil (Karlsruhe Institute of Technology), and (right) Daniel Hug (Karlsruhe Institute of Technology). At the minisymposium, Markus Kiderlen from CSGB also gave an invited talk.

SUMMER SCHOOL IN AALBORG 2013

Summer school on space-time modeling and inference

Aalborg University, Department of Mathematical Sciences, 27-31 May 2013

Teaching team

- Professor **Peter Diggle**, Lancaster University
- Professor **Tilmann Gneiting**, University of Heidelberg
- Professor **Peter F. Craigmile**, University of Glasgow
- Professor **Rasmus Waagepetersen**, Aalborg University

Themes

1. space-time point processes
2. correlation theory of stochastic processes
3. spectral- and wavelet-based methods including time-frequency representations
4. spatial Gibbs and Cox point processes

Scope of the Summer School

Professor Peter Diggle, Lancaster University, will give a simple classification of space-time point processes and/or data according to whether the spatial or temporal dimension (but not both!) is discrete, and argue that these different situations require different approaches to statistical analysis. The choice of modelling strategy should be influenced by the scientific goals of the study that generated the data for analysis. He will also describe statistical models, methods and R packages for space-time point process data.

Professor Tilmann Gneiting, University of Heidelberg, will discuss the correlation theory of stochastic processes on Euclidean domains and spheres, which offers a wide range of challenging open problems. Applications and case studies in weather and climate research call for an increased involvement of probabilists and statisticians in the atmospheric sciences.

Professor Peter F. Craigmile, University of Glasgow, will introduce spectral- and wavelet-based methods that can be applied to temporal, spatial, and spatiotemporal data. Topics include time-frequency representations, model construction, and approximate methods of inferences for spatio-temporal processes.

Professor Rasmus Waagepetersen, Aalborg University, will consider statistical models and methods for spatial point processes. His lectures will provide an introduction to spatial Gibbs and Cox point processes and to various approaches to inference for spatial point processes including summary statistics, estimating functions and maximum likelihood estimation.

Target

Ph.D.-students and postdocs with an interest in spatial statistics.

More information: www.csgb.dk

CSGB RESEARCH REPORTS 2012

CSGB has its own research report series that mainly publishes mathematical and statistical manuscripts. The major part of these manuscripts will later appear in international journals. The publication traditions are different in computer science and biology for which reason publications written by CSGB researchers from these fields will appear directly in international journals, proceedings, etc.

1. Auneau-Cognacq, J., Ziegel, J. & Jensen, E.B.V. (2012): Rotational integral geometry of tensor valuations. *CSGB Research Report* **12-02**. To appear in *Adv. Appl. Math.*

2. Coeurjolly, J.-F. and Rubak, E. (2012): Fast covariance estimation for innovations computed from a spatial Gibbs point process. *CSGB Research Report* **12-03**. To appear in *Scand. J. Statist.*

3. Coeurjolly, J.-F. & Møller, J. (2012): Variational approach for spatial point process intensity estimation. *CSGB Research Report* **12-09**. Submitted.

4. Dvořák, J. & Jensen, E.B.V. (2012): On semi-automatic estimation of surface area. *CSGB Research Report* **12-06**. To appear in *J. Microsc.*

5. Hansen, L.V. & Thorarinsdottir, T.L. (2012): A note on moving average models for Gaussian random fields. *CSGB Research Report* **12-13**. Submitted.

6. Jensen, E.B.V. & Jónsdóttir, K.Ý. (2012): Lévy-based modelling in circular systematic sampling. *CSGB Research Report* **12-10**. Submitted.

7. Jensen, E.B.V. & Ziegel, J.F. (2012): Local stereology of tensors. *CSGB Research Report* **12-11**. Submitted.

8. Jensen, J.L., Raarup, M.K. & Rubak, E. (2012): Estimating protein-protein interaction affinity in single living cells using Förster resonance energy transfer measurements. *CSGB Research Report* **12-12**. Submitted.

9. Lavancier, F., Møller, J. & Rubak, E. (2012): Statistical aspects of determinantal point processes. *CSGB Research Report* **12-04**. Submitted.

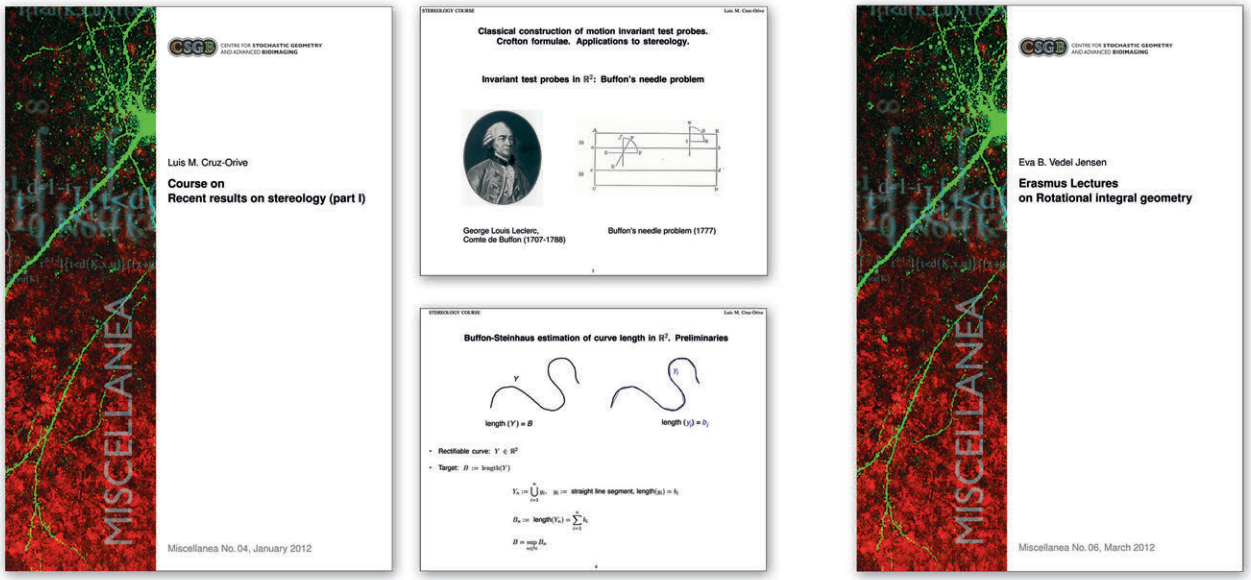
10. Møller, J. & Toftaker, H. (2012): Geometric anisotropic spatial point pattern analysis and Cox processes. *CSGB Research Report* **12-01**. Submitted.

11. Svane, A.M. (2012a): Local digital algorithms for estimating the mean integrated curvature of r-regular sets. *CSGB Research Report* **12-08**. Submitted.

12. Svane, A.M. (2012b): Local digital estimators of intrinsic volumes for Boolean models and in the design based setting. *CSGB Research Report* **12-07**. Submitted.

13. Thórisdóttir, Ó. & Kiderlen, M. (2012): Wicksell's problem in local stereology. *CSGB Research Report* **12-05**. To appear in *Adv. Appl. Probab.*

CSGB Research Reports 2012 can be downloaded at www.csgb.dk/publications/csgbrr/2012/.



CSGB Miscellanea 2012 can be downloaded at www. csgb.dk/publications/miscellanea/.

CSGB MISCELLANEA 2012

The CSGB miscellanea series contains various internal publications such as lecture notes, conference abstracts, etc. Three such publications appeared in 2012.

1. Cruz-Orive, L.M. (2012a): Course on recent results in stereology (part I). *CSGB Miscellanea* **04**. 32 pages.

2. Cruz-Orive, L.M. (2012b): Course on recent results in stereology (part II). *CSGB Miscellanea* **05**. 31 pages.

3. Jensen, E.B.V. (2012): Erasmus lectures on rotational integral geometry. *CSGB Miscellanea* **06**. 17 pages.

Fifth Internal CSGB workshop – Dragør

The internal CSGB workshops are held twice a year. They are arranged alternately by the two Aarhus groups (the stochastic geometry group and the biomedical group), the spatial statistics group at Aalborg University and the image group at University of Copenhagen.

The aim of these internal workshops is to discuss the present status of the CSGB research projects by presentations by the members of CSGB and to plan the further progress of the research projects. Furthermore, new activities arranged by CSGB such as workshops, courses, establishment of new international contacts, etc. are also discussed at these internal workshops. The fifth internal workshop was arranged by the Image group and took place at Dragør Badehotel, 24 - 25 May 2012.

CSGB JOURNAL AND PROCEEDINGS PUBLICATIONS, BOOK CHAPTERS

Kubb competition

Auneau, J., Rataj, J. & Jensen, E.B.V. (2012): Closed form of the rotational Crofton formula. *Math. Nachr.* **285**, 164-180.

Brandt, S.S., Jensen, K.H. & Lauze, F.B. (2012): Bayesian epipolar geometry estimation from tomographic projections. *11th Asian Conference on Computer Vision, South Korea.*

Chen, C., Lauze, F.B., Igel, C., Feragen, A., Loog, M. & Nielsen, M. (2012): Towards exaggerated image stereotypes. In: *Proceedings of The First Asian Conference on Pattern Recognition 2011*, Beijing, China, p. 422-426.

Chen, C., Sørensen, L.E.B.L., Lauze, F.B., Igel, C., Loog, M., Feragen, A., de Bruijne, M. & Nielsen, M. (2012): Towards exaggerated emphysema stereotypes. In: *SPIE Medical Imaging 2012*. San Diego, USA: SPIE - International Society for Optical Engineering.

Chen, F., Wegener, G., Madsen, T.M. & Nyengaard, J.R. (2012): Mitochondrial plasticity of the hippocampus in a generic rat model of depression after antidepressant treatment. *Synapse* **67**, 127-134.

Crimi, A., Loog, M., de Bruijne, M., Nielsen, M. & Lillholm, M. (2012): Shape-based assessment of vertebral fracture risk in postmenopausal women using discriminative shape alignment. *Academic Radiology* **19**, 446-454.

Darkner, S. & Sporring, J. (2012): Locally orderless registration. *IEEE Transactions on Pattern Analysis and Machine Intelligence.* Published online 26 October 2012.

Feragen, A. (2012): Topological stability through extremely tame retractions. *Topology and Its Applications* **159**, 457-465.

Feragen, A., Petersen, J., Owen, M., Lo, P., Hohwu, L., Wille, M., Dirksen, & de Bruijne, M. (2012): A hierarchical scheme for geodesic anatomical labeling of airway trees. *Proceedings of MICCAI 2012*, 147-155.

Gorbunova, V., Sporring, J., Lo, P., Loeve, M., Tiddens, H.A., Nielsen, M., Dirksen, A. & de Bruijne, M. (2012): Mass preserving image registration for lung CT. *Medical Image Analysis* **16**, 786-795.

Hahn, U. (2012). A studentized permutation test for the comparison of spatial point patterns. *J. Amer. Statist. Assoc.* **107**, 754-764.

Hauberg, S., Lauze, F.B. & Pedersen, K.S. (2012): Unscented Kalman filtering on Riemannian manifolds. *Journal of Mathematical Imaging and Vision.* Published online DOI 10.1007/s10851-012-0372-9.

Hauberg, S., Sommer, S.H. & Pedersen, K.S. (2012): Natural metrics and least-committed priors for articulated tracking. *Image and Vision Computing* **30**, 453-461.

Jalilian, A., Guan, Y. & Waagepetersen, R. (2012): Decomposition of variance for spatial Cox processes. *Scand. J. Statist.* **40**, 119-137.

Kaae, S.S., Chen, F., Wegener, G., Madsen, T.M. & Nyengaard, J.R. (2012): Quantitative hippocampal structural changes following electroconvulsive seizure treatment in a rat model of depression. *Synapse* **66**, 667-676.

Kampf, J. (2012): The parallel volume at large distances. *Geometriae Dedicata* **160**, 47-70.

Kiderlen, M. (2012): Introduction to integral geometry and stereology. In: Springer LNM **2068** on *Stochastic Geometry, Spatial Statistics and Random Fields*, ed. E. Spoderev, Springer, Heidelberg.

Kristiansen, S.L & Nyengaard, J.R. (2012): Digital stereology. *APMIS* **120**, 327-340.

Miller, T., van Colen, G., Sander, B., Golas, M.M., Uezguen, S., Weigandt, M. & Goepferich, A. (2012): Drug loading of polymeric micelles. *Pharm Res.* Published online DOI 10.1007/s11095-012-0903-5.

Moyer, C.E., Delevich, K.M., Fish, K.N., Asafu-Adjei, J.K., Sampson, A.R., Dorph-Petersen, K.-A., Lewis, D.A. & Sweet, R.A. (2012): Reduced glutamate decarboxylase 65 protein within primary auditory cortex inhibitory boutons in schizophrenia. *Biol Psychiatry* **72**, 734-743.

Møller, J. & Berthelsen, K.K. (2012): Transforming spatial point processes into Poisson processes using random superposition. *Adv. Appl. Probab.* **44**, 42-64.

Møller, J. & Ghorbani, M. (2012): Aspects of second-order analysis of structured inhomogeneous spatio-temporal point processes. *Statistica Neerlandica* **66**, 472-491.

Møller, J. & Rasmussen, J.G. (2012): A sequential point process model and Bayesian inference for spatial point patterns with linear structures. *Scand. J. Statist.* **39**, 618-634.

Prasoon, A., Igel, C., Loog, M., Lauze, F.B., Dam, E. & Nielsen, M. (2012): Cascaded classifier for large-scale data applied to automatic segmentation of articular cartilage. In: *SPIE Medical Imaging 2012.* SPIE - International Society for Optical Engineering.

Prokešová, M. & Jensen, E.B.V. (2012): Asymptotic Palm likelihood theory for stationary point processes. *Ann. Inst. Statist. Math.* Published online DOI 10.1007/s10463-012-0376-7.

Raket, L.L. & Nielsen, M. (2012): A splitting algorithm for directional regularization and sparsification. In: *Proc. International Conference on Pattern Recognition. IEEE Communications Society*, 1-5.

Sommer, S.H., Lauze, F., Nielsen, M. & Pennec, X. (2012): Kernel bundle EPDiff: evolution equations for multi-scale diffeomorphic image registration. *Proceedings of the Third International Conference on Scale Space and Variational Methods in Computer Vision*, 677-688.

Sommer, S.H., Nielsen, M. & Pennec, X. (2012): Sparsity and scale: compact representations of deformation for diffeomorphic registration. *MMBIA Workshop at WACV 2012*, Breckenridge, Colorado.

Sørensen, L.E.B.L., Nielsen, M., Lo, P.C.P., Ashraf, H., Pedersen, J.J.H. & de Bruijne, M. (2012): Texture-based analysis of COPD: a data-driven approach. *IEEE Transactions on Medical Imaging* **31**, 70-78.

CSGB excursion to Kollinghus Castle

CSGB SEMINARS

16 February 2012 | Sami Brandt (University of Copenhagen): **On the probabilistic multi-view geometry**

16 February 2012 | Markus Kiderlen (Aarhus University): **Reconstruction of convex sets from support- or brightness functions**

1 March 2012 | Johanna Ziegel (Heidelberg University): **Lévy based isotropic random fields on spheres**

15 March 2012 | Toshiya Hachisuka (Department of Computer Science, Aarhus University): **Realistic image synthesis using computational statistics**

16 March 2012 | Linda Udby (Niels Bohr Institute, University of Copenhagen): **Visions for data analysis software at ESS**

19 April 2012 | Jean-François Coeurjolly (Grenoble University): **About the multivariate fractional Brownian motion**

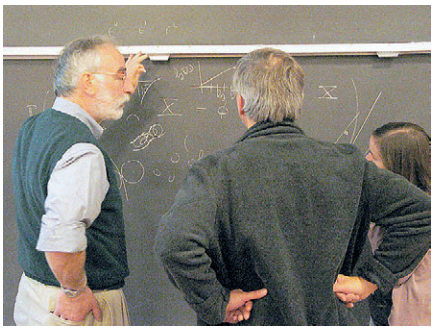
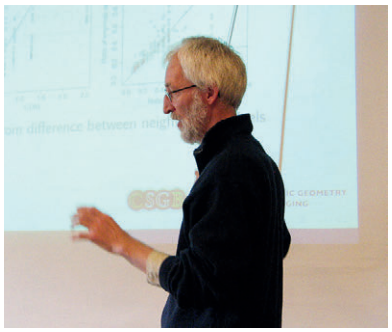
11 May 2012 | Robert Feidenhans'l (Niels Bohr Institute, University of Copenhagen): **Data analysis in real time?**

21 May 2012 | Gopalan Nair (University of Western Australia): **Analysis of point processes on a linear network**

31 May 2012 | Michaela Prokešová (Charles University, Praha): **Statistical analysis of Lévy driven Cox point processes - spatial and spatio-temporal**

12 June 2012 | Gopalan Nair (University of Western Australia): **Analysis of multivariate point processes on a linear network**

20 June 2012 | Richard J. Gardner (Western Washington University, USA): **What's so special about Minkowski addition?**

Minisymposium on the occasion of the Midterm Evaluation of CSGB, 13 October 2012, Aarhus

CSGB was established on 1 April 2010. On 13 October 2012, a minisymposium was held at Department of Mathematics, AU, on the occasion of the Midterm Evaluation of CSGB. The aim of this minisymposium was to present and discuss some of the most important research results obtained so far. The advisory board of CSGB attended this minisymposium. Seven scientific talks were given on this occasion. At the end of the day the future research plans was discussed between members of the advisory board and the research group leaders.

Workshop on Geometry and Statistics: Manifolds and Stratified Spaces, 8-12 October 2012, Sandbjerg Estate

This **interdisciplinary workshop** (co-financed by an International Network Programme grant from the Danish Council of Scientific Research and Innovation) brought together scientists from mathematics, statistics, computer science and engineering with a special interest in bioimaging. An important motivation for organizing this workshop was the need for a closer contact between theoretical mathematicians/statisticians developing statistical methods for data on manifolds and stratified spaces, and computer scientists/engineers dealing with concrete bioimaging applications. Tree-space statistics was among the main topics of the workshop.

On the basis of the talks at the workshop, a special issue of **Journal of Mathematical Imaging and Vision** (JMIV) is planned. The special issue is aimed as an overview of current results and problems from geometry and statistics of nonlinear data spaces, to serve as a coherent source of information for the broader statistics and imaging communities.






CSGB VISITORS

From fifth internal CSGB workshop

Arulmani Manavalan (University of Madras, India)
1 January – 31 August, 2012

Jiri Dvořák (Charles University, Czech Republic)
4 January – 21 June, 2012

Rolf Krause (Università della Svizzera Italiana, Lugano, Switzerland), 30 January - 3 February, 2012

Michael Ulbrich (Technical University of Munich, Germany), 30 January - 3 February, 2012

Jean-Francois Coeurjolly (Grenoble University)
1 February – 31 July, 2012

Johanna Ziegel (Institute for Applied Mathematics and Statistics, Heidelberg University, Germany)
19 February – 2 March, 2012

Michael Brady (Department of Oncology, Oxford, United Kingdom), 12 - 13 March, 2012

Carla van Gils (Julius Center for Health Sciences and Primary Care, Epidemiology UMC Utrecht)
12 - 13 March, 2012

Jan Rataj (Charles University, Praha, Czech Republic)
19 – 30 March, 2012

Sarang Joshi (Department of Bioengeneering, University of Utah, US), 28 - 29 March, 2012

Alain Trouvé (Centre de Mathematiques et Leurs Applications, Ecole Normale Superieure, Cahan, France) 28 - 29 March, 2012

Frédéric Lavancier (University of Nantes)
30 March – 6 April, 2012

Tim Cootes (Human and Medical Sciences, University of Manchester, United Kingdom), 1 - 2 May, 2012

Milan Sunka (Dept. of Electrical and Computer Engineering, University of Iowa, US), 1 - 2 May, 2012

Yongtao Guan (University of Miami)
1 May – 30 June, 2012

Sunday Abraham Musa (Ahmadu Bello University, Nigeria), 1 May – 31 October, 2012

Gopal Nair (The University of Western Australia, Australia), 13 May – 23 June, 2012

Sharmila Mujamdar (Dept. of Bioengineering, UC Berkeley, US), 18 - 19 May, 2012

Sebastien Ourselin (University College London, United Kingdom), 18 - 19 May, 2012

Michaela Prokešová (Charles University, Czech Republic), 28 May – 8 June, 2012

Richard J. Gardner (Western Washington University, USA), 1 – 26 June, 2012

Koen van Leemput (Department of Radiology, Massachusetts General Hospital, US), 5 - 8 June, 2012

Johannes Lotz (Institute of Mathematics and Image Computing, University of Lübeck, Germany)
5 - 8 June, 2012

Marc Modat (University College London, United Kingdom), 5 - 8 June, 2012

Jan Modersitzki (Institute of Mathematics and Image Computing, University of Lübeck, Germany)
5 - 8 June, 2012

Sebastien Ourselin (University College London, United Kingdom, 5 - 8 June, 2012

Hans Henrik Thodberg (Visiana ApS, Denmark)
5 - 8 June, 2012

Daniel Hug (Karlsruhe Institute of Technology, Germany), 5 – 9 June, 2012

Wolfgang Weil (Karlsruhe Institute of Technology, Germany), 6 – 9 June, 2012

Marleen de Bruijne (Biomedical Imaging Group, Erasmus MC Rotterdam, the Netherlands)
20 - 24 August, 2012

Corinna Cortes (Head of Google Research New York, US), 20 - 24 August, 2012

Trevor Darrell (CS Division, University of California, Berkeley, US), 20 - 24 August, 2012

Tobias Glasmachers (Institut für Neuroinformatik, Ruhr-Universität Bochum, Germany), 20 - 24 August, 2012

Marco Loog (Pattern Recognition Laboratory, Delft University of Technology, the Netherlands)
20 - 24 August, 2012

Yishay Mansour (School of Computer Science, Tel Aviv University, Israel), 20 - 24 August, 2012

Mehryar Mohri (Institute of Mathematical Sciences, New York, US), 20 - 24 August, 2012

Angelika Nowak (Silesia Universitet, Poland)
17 September – 7 December, 2012

Håkon Toftaker (Norwegian University of Science and Technology), 24 – 28 September, 2012

James Damon (University of North Carolina, USA)
7 – 12 October, 2012

Herbert Edelsbrunner (Duke University, USA; Institute of Science and Technology, Austria),
7 – 12 October, 2012

Stephan Huckemann (Georgia Augusta University Göttingen, Germany), 7 – 12 October, 2012

Sarang Joshi (University of Utah, USA)
7 – 12 October, 2012

Steve Marron (University of North Carolina, USA)
7 – 12 October, 2012

Peter W. Michor (Universität Wien, Austria)
7 – 12 October, 2012

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7 – 12 October, 2012

Megan Owen (University of Waterloo, USA)
7 – 12 October, 2012

Xavier Pennec (INRIA Sophia-Antipolis, France)
7 – 12 October, 2012

Steven W. Zucker (Yale University, USA)
7 – 14 October, 2012

Hans Hebert (Karolinska Institutet, Sweden)
12 - 14 October, 2012

Håvard Rue (Norwegian University of Science and Technology, Trondheim, Norway)
12 – 14 October, 2012

Aikaterini Liakou (Dessau Medical Centre, Dessau, Germany), 3 – 10 December, 2012

Michaela Prokešová (Charles University, Czech Republic), 9 – 14 December, 2012

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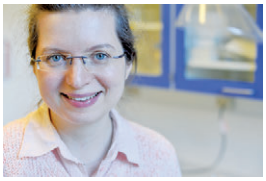
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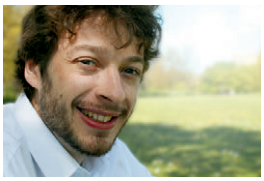
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CENTRE FOR **STOCHASTIC GEOMETRY**
AND ADVANCED **BIOIMAGING**

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